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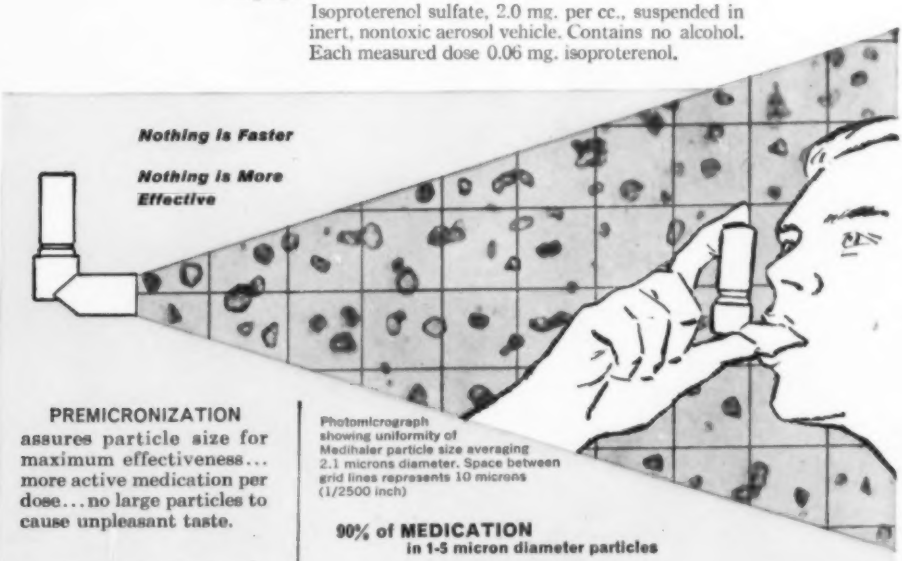

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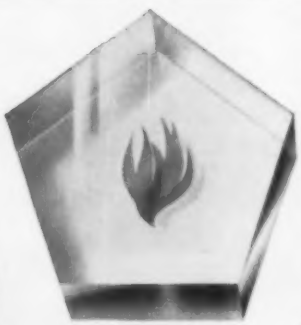

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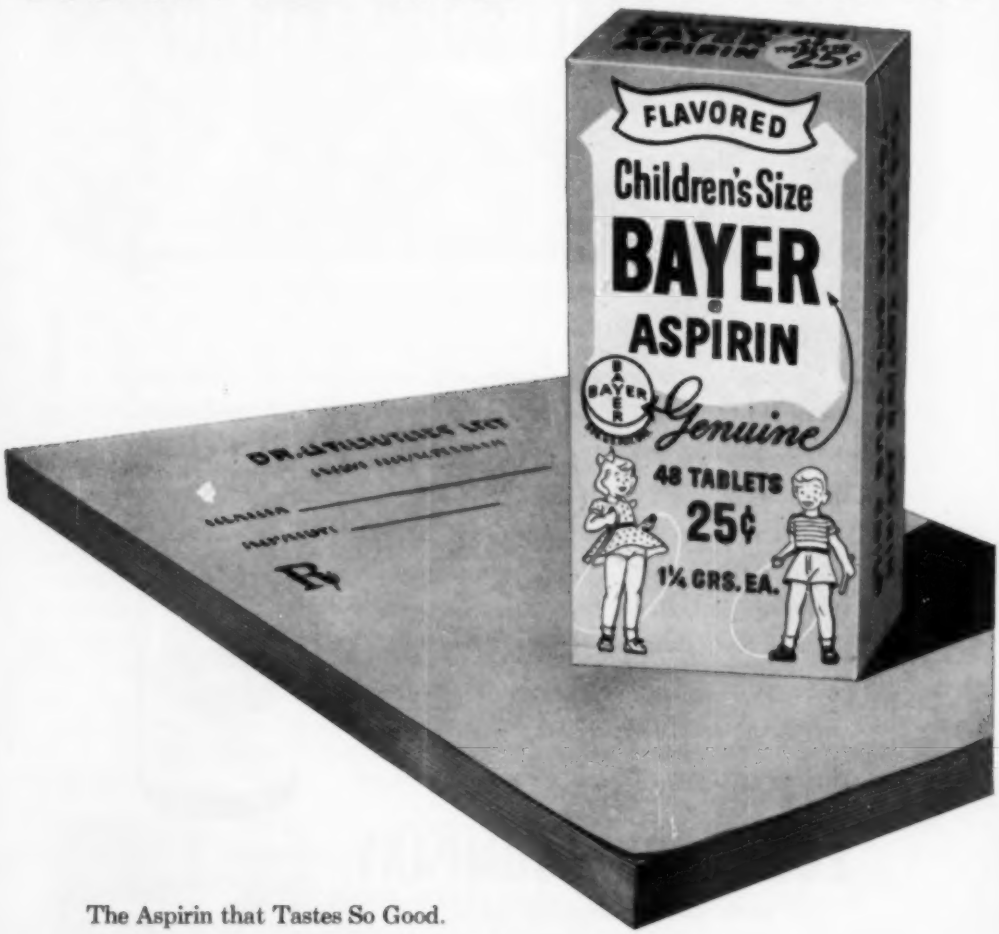

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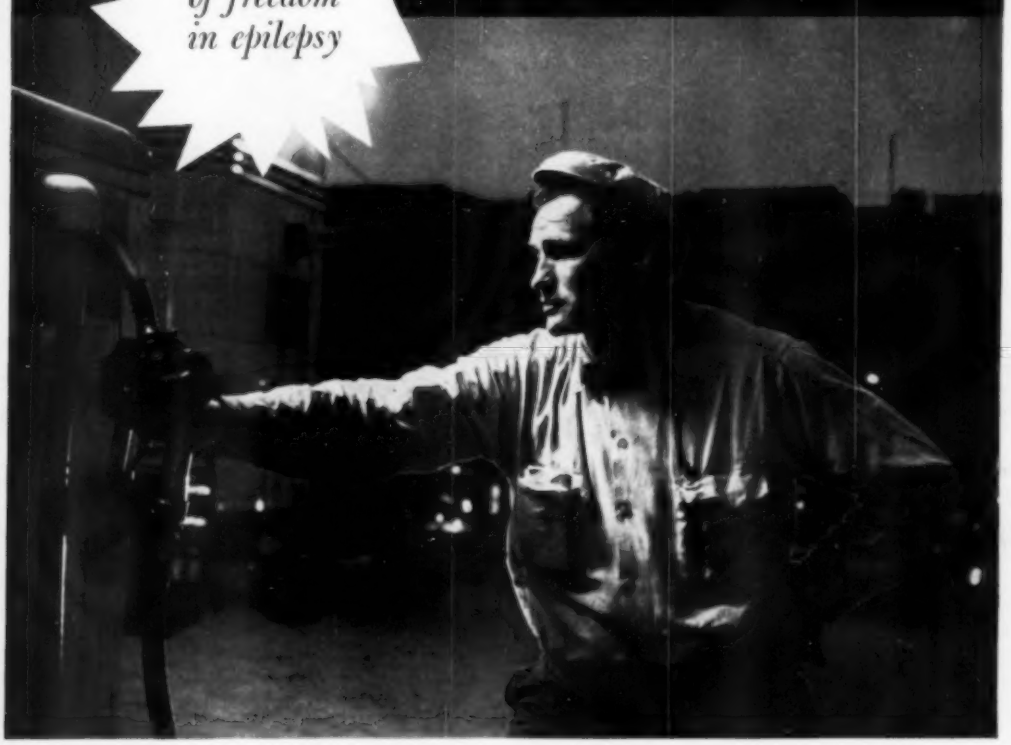

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DISEASES OF CHILDREN

Mental Development of Children with Blindness Due to Retrolental Fibroplasia

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It has been amply demonstrated that some children who are blind as a result of retrolental fibroplasia have normal mental development,[1,2] and there is some evidence that the majority of these children have normal mental development.[2-5] On the other hand, other observers have noted a high incidence of mental retardation associated with retrolental fibroplasia and also a high incidence of neurological disorders.[6-8] The problem is further complicated by the fact that blindness due to retrolental fibroplasia essentially occurs only in premature infants. It has long been known that cerebral palsy and other neurological disorders occur more frequently in premature infants than in full-term infants.[9-12] Some[11,12] also take a pessimistic view of the mental development of all premature infants, although most investigators have demonstrated that this is unwarranted, as indicated in the extensive review by Alm[9] and in the work of Hess, Mohr, and Bartelme.[13]

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Since retrolental fibroplasia has been demonstrated to be primarily due to oxygen poisoning,[14-16] there is great concern that oxygen poisoning may also be a factor in the development of mental retardation and neurological disorders in premature infants.[7,17,18]

An additional complication is the intense emotional reaction of the parents of blind children and of society in general toward these children so that pseudo mental retardation may readily be created through environmental limitations.[2,19,20]

The comparison of a group of children blind as a result of retrolental fibroplasia with a group of children blind as a result of other causes seemed a logical approach in attempting to discern the possible adverse effects of oxygen on the neurological and mental development of premature infants.

To eliminate as much as possible the factor of institutional pseudoretardation or environmental pseudoretardation in the home, or at least to document this when present, it was decided to include only those children known to the staff of the California School for the Blind, henceforth referred to as the Field Service for preschool blind children. The purpose of this service is to assist and instruct the parents in the early care and training of their children and to do everything to promote the child's

physical, mental, and social development. Obviously, there are practical and human limitations to the extent to which this can be accomplished. Nevertheless, many blind children and their parents seem to benefit from this service. The service does not continue after the child enters school, since counseling services are provided through the school at that time. It was, however, necessary to include some children not known to this service until nearly school age and also some children who entered institutions early in the preschool period.

It was further decided to study only school-age children. At this age the weeks of prematurity do not enter significantly into the calculation of the intelligence quotient nor in other estimations of performance. Furthermore, it was felt that school adjustment and performance could be used as a method of evaluating mental development and perhaps in some instance might be more valid than intelligence test results.

Materials and Methods

The staff of the Field Service for blind preschool children of the California School for the Blind collected data on cases known to them and living in the Los Angeles area. This was done in the spring of 1955, and all of the children were between the ages of 5 years 9 months and 9 years 9 months at that time. All were chronologically eligible for public elementary school, although not all were in school. A few were still in nursery schools because of social immaturity, and others were in the state hospital for the mentally retarded because of severe mental retardation.

The type of elementary school attended by these children was variable. Some attended the state residential School for the Blind, some segregated day schools for the blind, and other schools with integrated programs for blind children and sighted children. Similarly, some had attended residential nursery schools, segregated nursery schools for the blind, and integrated nursery schools for the blind and sighted children. Insofar as possible the type of school attended is indicated in the case summaries.

The schools were very cooperative in submitting reports of school progress and intelligence test results when available. The type of intelligence test used was not always indicated. The intelligence test results submitted to us by the Los Angeles Board of Education were obtained with the Interim Hayes-Binet test.

The medical data regarding the diagnosis of the eye condition, amount of vision, the birth weight, and length of gestation were obtained from the parents. However, as often as possible diagnoses were obtained directly from the child's physician. It is recognized that some of the diagnoses as indicated are incomplete or tentative. A child is considered legally blind if the vision in his best eye is 20/200 or less with correction.

All this information was summarized along with the notes of the staff members of the Field Service for blind preschool children. From this data judgments were made as to the probable normalcy of mental development of each child. The children were classified as either normal or mentally retarded. Any child with a recorded intelligence test result of less than 70 was considered mentally retarded, and all those recorded above 70, as normal.

It is recognized that there may be differences of opinion on some of the decisions made; therefore, the case summaries are included in this report for evaluation by others.

Results

This study includes 38 children born prematurely and blind as a result of retrolental fibroplasia. Their mental development and progress in school is compared with those of 22 children blind owing to causes other than retrolental fibroplasia. All but five of the latter children were born at term.

The comparison of these two groups as to normalcy of mental development (Table 1) revealed 12, or 32%, of the children blind as a result of retrolental fibroplasia and 9, or 41%, of the children blind owing to other causes to be mentally retarded. The difference in the incidence of mental

TABLE 1.—*General Evaluation of Mental Development*

Mental Development	Blindness Due to					
	RLF		Other Causes		All Causes	
	No.	%	No.	%	No.	%
Normal	26	68	13	59	39	65
Mentally retarded	12	32	9	41	21	35
Totals	38	100	22	100	60	100

$P>0.5$ as calculated by the χ^2 method.

TABLE 2.—*Type of Schooling at the Time of Reporting*

Blindness Due to	State Hosp. for Ment. Ret. or Applicant		In Special School for Ment. Ret. or No School		Segregated School for Blind		School with Integrated Program for Blind & Sighted		Residential School for Blind & Sighted		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
RLF	4	10.5	6	15.7	7	18.3	13	34.2	8	21.0	38	100
Other causes	2	9.1	5	22.7	5	22.7	7	31.8	3	13.6	22	100
Totals	6	10.0	11	18.3	12	20	20	33.3	11	18.6	60	100

retardation between these two groups is not statistically significant as calculated by the χ^2-method ($P>0.5$).

Further detailed analysis of the two groups does not significantly alter the number of children considered mentally retarded in either group.

Of the children with blindness due to retrolental fibroplasia 10, or 26.2%, and of those blind as a result of other causes 7, or 31.7%, were either in a state institution for the mentally retarded, had applied for admission to such an institution, or were in a private school for the mentally retarded or were too retarded to attend school and were at home (Table 2).

A surprising number of children of both groups attended school with integrated programs for the blind with sighted children, 13, or 34.2%, of those with blindness due to retrolental fibroplasia and 7, or 31.8%, of those with blindness due to other causes. Thus, nearly half, or 20 (46%) of the 43 children who are attending school and are not in schools for retarded children are in schools with integrated programs.

There is insufficient material to evaluate the different types of schooling in terms of the child's mental development, and many selective factors are involved in the admission of children to the various schools.

An analysis of the mental evaluation of those children considered to have normal intelligence (Table 3) revealed 14 of the children with blindness due to retrolental fibroplasia had reported intelligence test results above 70 except 1 (Case 21). This child's intelligence test results were reported simply as less than 80, but the tester's comment was that he was probably normal. His school progress also suggested this. Twelve children were evaluated as mentally normal on the basis of history of progress at home and in school. In three instances (Cases 25, 32, and 38) there might be some doubt as to the intelligence level being greater than 70, but these children were not considered mentally retarded by those who worked with them.

Of the children blind as a result of other causes who were considered to have normal intelligence, six had reported intelligence test scores and seven were evaluated by history of progress at home and at school. Of the latter group, there was one (Case 52) about whom there were conflicting opinions as to normalcy of development. However, the latest school reports were satisfactory.

TABLE 3.—*Analysis of the Evaluation of Intelligence of Children Considered Normal*

Method of Evaluation	Mental Evaluation	RLF	Other Causes	Totals
Intelligence test scores	130+	0	1	
	110-129	4	0	
	90-109	7 *	3	
	70-89	3 †	2	
No. tested		14	6	20
Evaluation by history	Definite	9	6	
	Questionable	3	1	
No. not tested		12	7	19
Total		26	13	39

* Three children in this group were considered emotionally very disturbed with possible better potential (Cases 3, 6, and 22).

† One child was simply reported as having intelligence of less than 80, but tester's comment was "probably normal" and progress had been fair (Case 21).

TABLE 4.—*Analysis of the Evaluation of Children Considered Mentally Retarded*

Method of Evaluation	Mental Evaluation	Blindness Due to: RLF	Blindness Due to: Other Causes	Totals
Intelligence test	Less than 70	1 *	1 †	
Evaluation by history	Definite Emotional disturbance	8	7	
	Environmental deprivation	1		
	Deaf & blind	1	2	
Total		12	9	20

* Intelligence score reported as less than 80. Clinically, child is emotionally disturbed and making poor progress (Case 20).
† Intelligence score reported as less than 70, but there is good academic progress (Case 40).

The result of this analysis would suggest that the consideration of 26, or 68%, of 38 children with blindness due to retrolental fibroplasia as probably having intelligence above 70 is justified. Similarly, that the consideration of 13, or 59%, of 22 children with blindness due to other causes as probably having intelligence above 70 is justified.

An analysis of the evaluation of the children considered mentally retarded revealed that intelligence test scores were available for only two of these children, and both of these were given qualified scores by the examiner. The child with blindness due to retrolental fibroplasia had an intelligence test score reported as less than 80. Clinically, he is described as making poor progress and as emotionally disturbed (Case 20). Although it seems clear that he is functioning at a level probably less than 70, it is entirely possible that emotional factors were operative in causing only apparent retardation. On the other hand, the child blind as a result of other causes had an intelligence test score of less than 70 but was making good academic progress, suggesting this test score might be in error.

Of the 11 children blind as a result of retrolental fibroplasia with no intelligence tests reported, three were considered very emotionally disturbed and one was deaf as well as blind. In all four of these instances it would be difficult to be sure that the children do not have greater potential for mental development than they exhibited. On the other hand, none of the nine children with blindness due to other causes and mentally retarded was described as severely emotionally disturbed, but two children were deaf as well as blind. It is felt that the mental potential of the latter two children could not be evaluated, although functionally they are severely retarded.

It seems plausible that some children have been classified as mentally retarded who have greater potential than is functionally demonstrated, because of emotional problems or deafness. This group seems larger among those blind as a result of retrolental fibroplasia.

Of possible significance is the finding that seven of the children blind as a result of retrolental fibroplasia were described as significantly emotionally disturbed. Three of these children had intelligence test scores of over 90 (Cases 3, 6, and 22), and one (Case 21) is reported as scoring less than 80 on an intelligence test but was considered as probably normal by the tester. A fifth child (Case 38) was not tested, but despite his emotional problems he seems to be doing well in school. The remaining two children were classified as mentally retarded. One child (Case 20) had an intelligence test reported as less than 80 and progress in school reported as very satisfactory. The other child (Case 4) had been emotionally and environmentally deprived during his early life and had retreated from the world. It is felt that his retardation could be entirely emotional. Another child (Case 23), not described as emotionally disturbed, was considered as possibly only functionally retarded because of limited environment.

Only one of the children (Case 56) with blindness due to causes other than retrolental fibroplasia was described as significantly emotionally disturbed. This child

had had encephalitis resulting in optic atrophy. Her intelligence was considered average. None of the children classified as mentally retarded in this group were considered to be so on an emotional basis, except possibly Case 40. This child had a reported IQ of less than 70, had a limited environment in early life, but was doing well in school.

The difference between the two groups in terms of emotional problems recorded is striking. This suggests that some special factor is operative, unique either to children of premature birth or to children with blindness due to retrolental fibroplasia or both. This could be due to a disturbance in the mother-child relationship [2,19,20] or to some organic cerebral problem associated with prematurity [21] or to the oxygen poisoning that also caused the retrolental fibroplasia. It would not seem to be related to blindness alone, since the frequency of emotional problems was so much less in the group of infants blind as a result of other causes. It should be pointed out, however, that the size of both groups is small, and so this difference may not be significant.

An analysis of the relationship of stated causes of blindness other than retrolental fibroplasia and mental retardation was attempted (Table 5). The number of cases is too small to draw any definite conclusions, but certain trends seem worthy of comment.

Of particular interest is the fact that six, or two-thirds, of all of the mentally retarded cases were associated with optic atrophy as the cause of blindness. Of the three remaining mentally retarded children in this group, one had congenital cataracts and deafness and another was listed as having congenital eye defect and deafness. Thus, if one considers optic atrophy or deafness as neurological disorders in these patients, all but one of the mentally retarded children in this group had evidence of a neurological lesion either as the direct cause of the blindness or as associated deafness.

TABLE 5.—*Analysis of the Cause of Blindness Other Than Retrolental Fibroplasia and the Incidence of Mental Retardation*

Cause of Blindness	No.	Mental Status Normal *	Mentally Defective *
1. Optic atrophy	9	3(P)	6
2. Cong. cataracts	3	2	1(D)
3. Microphthalmos	2	2(P?)	
4. Retinoblastoma	2	2	
5. Glaucoma	1	1	
6. Severe myopia	1	1	
7. Cong. eye defect & deafness	1		1(D)
8. Glioma and iritis	1	1(P)	
9. Cong. retinal fold	1	1(P)	
10. Retinal detachment	1		1(P)
Totals	22(100%)	13(59%)	9(41%)

* P, premature birth of one child in diagnostic group; D, additional handicap of deafness; ?, doubt as to normalcy of the one child born prematurely.

Of further interest is the finding that of the five premature infants in this group only one is definitely mentally retarded, though there is some question about one other child. Thus, prematurity as such did not contribute significantly to the incidence of mental retardation in this group. Of concern is the possibility that the diagnoses listed as glioma and iritis, congenital retinal fold, and retinal detachment, all in premature infants, might have been misdiagnosed retrolental fibroplasia. There was insufficent information to evaluate this possibility.

Comment

The findings of this study confirm in general the findings of others [2-5] that children with blindness due to retrolental fibroplasia show no greater incidence of mental retardation than do children blind from other causes. However, the incidence of mental retardation is higher in both groups (Table 1) of children in this study than is generally reported. This may be due to the small number of children in this study in comparison with some of the other studies. It is possible that some of these children are only functionally retarded,

TABLE 6.—*Case Summaries of Children Blind As a Result of Retrolental Fibroplasia (RLF)*

Case No.	Age Group	Diagnosis & Estimated Amount of Vision	Birth Weight	Length of Gestation, Mo.	Sex	Intelligence Classification	Comments
1	8 yr. 9 mo. to 9 yr. 9 mo.	RLF, light perception	2 lb.	6	M	IQ 90-109 Hayes-Binet	Sat and rocked most of first 4 yr. before seen by staff of F. S. B. C. *; good cooperation from parents once his needs were understood; very slow start at segregated school for the blind; now in 3d yr. & making good progress
2		RLF, no light perception	1 3/4 lb.	6	F	IQ 113	First seen by staff of F.S.B.C. at 3 yr. and showed good development then; an adopted child with good early home experiences; in 3d grade in an integrated school program with good adjustment
3		RLF, no light perception	1 lb.	6	F	IQ 90-109 Hayes-Binet	Seen first by F. S. B. C. at 4 yr. of age, child very "autistic"; has severe asthma; parents perfectionists; child had 4 yr. experience in a nursery school for the blind and is in second year of public segregated school for the blind; has demonstrated very slow progress, but steady improvement
4		RLF, no light perception	?	?	F	Mentally retarded	For first 6 mo. after diagnosis of blindness mother completely retreated from the world; child first seen by staff of F. S. B. C. at 4 yr. of age; they wondered if severe developmental retardation might be due to environmental deprivations rather than organic brain damage
5	7 yr. 9 mo. to 8 yr. 9 mo.	RLF, light perception	2 lb. 9 oz.	6	F	IQ 99	In 2d year in residential school for the blind, satisfactory adjustment has fulfilled earlier evidences of promise; had been overprotected, but parents have learned to give her more freedom and she has become adequately independent
6		RLF, light perception	?	?	M	IQ 96	Is in 3d year in an integrated public school; very disturbed child when he entered school, "autistic" and rejecting; has made a fair adjustment to school; IQ considered to be higher than recorded test results; family had no help with problem of blind child until child entered school
7		RLF, light perception	2 lb. 15 oz.	6	F	IQ 97	In 2d year in residential shcool for the blind; a good adjustment to school, after prolonged period of homesickness; had had 6 mo. in an integrated public school kindergarten previously
8		RLF	?	Prem.	F	Mentally retarded	
9		RLF, light perception	2 lb. 4 oz.	6	F	Mentally retarded	In a private school for the mentally retarded
10		RLF, light perception	2 lb.	6	M	Mentally retarded	Applicant for the state hospital for the mentally retarded
11		RLF, light perception	3 lb.	6	F	IQ 92	In 2d year in residential school for the blind; "has some difficulties because of frequent illness (asthma) and overprotective trends in the family; very slow progress"

* F. S. B. C., Field Service for blind preschool children.

TABLE 6.—*Case Summaries of Children Blind As a Result of Retrolental Fibroplasia (RLF)*—Continued

Case No.	Age Group	Diagnosis & Estimated Amount of Vision	Birth Weight	Length of Gestation, Mo.	Sex	Intelligence Classification	Comments
12		RLF, no light perception	1 lb. 8 oz.	5½ ?	F	IQ 77 Stanford-Binet	In first grade of an intergated public school program; had very limited experience until he started school; slow progress; it is belived his potential is greater than test indicated
13	7 yr. 9 mo. to 8 yr. 9 mo.	RLF	2 lb. 2 oz.	6	F	IQ 82	Rather limited experiences until in segregated residential nursery school for the blind for 2 yr.; now in 1st yr.in state residential school for the blind; after homesickness in early months became used to the school; slow progress, competent self care, but lack of initiative; the family seemed unable to help this child
14		RLF, useful vision	3 lb.	6½	M	Normal	In segregated public school, sight-saving classes; satisfactory school adjustment
15		RLF, light perception	2 lb. 8 oz.	6½	F	Normal	2d yr. in public school integrated kindergarten; slow but adequate progress
16		RLF, light perception	1 lb.+	6	F	IQ 110	Had 3 yr experience in an integrated nursery school starting at 2½ yr.; then 1 yr. in integrated kindergarten; now in 1st grade in integrated program; learning Braille; good promise fulfilled, "never know she was blind"
17		RLF	2 lb. 6 oz.	6	F	IQ 125	Had one year in integrated kindergarten; now in 1st year in residential school for the blind, "good adjustment—no difficulty whatsoever"
18		RLF, light perception	3 lb. 4 oz.	6½	M	IQ 120	First seen at 18 mo. by F. S. B. C. and showed advanced behavior & above-average adjustment then; parents responded to him, accepted and admired him, in 2d yr. of segregated public school with excellent school and general social adjustment
		RLF, profoundly deaf	?	Prem.	M	Mentally retarded?	In 3d year in residential school for the blind in deaf-blind program; impossible to obtain an IQ; general impression is that this child has capacity to learn
20		RLF, light perception	?	Prem.	F	80 Hayes-Binet, Mentally retarded	In 1st year in segregated public school program; academic progress has been unsatisfactory. Much irrelevant talk; had previously shown evidence of early "autism" with persistent echolalia; rejected by parents; had been in a residential nursery school for the blind 1 yr.; in preschool period had one severe prolonged convulsion said to have been a "cerebral accident"
21	7 yr. 9 mo. to 8 yr. 9 mo.	RLF, light perception	3 lb. 6 oz.	6½	M	80 Hayes-Binet; school considers potential as normal?	In 2d yr. in segregated public school; has had difficulty in adjusting and slow progress; school believes his intelligence is probably normal because of improvement; twin also blind but progressed more rapidly and was favored child; this boy showed great deal of hostility & resistance to adults

TABLE 6.—*Case Summaries of Children Blind As a Result of Retrolental Fibroplasia (RLF)*—Continued

Case No.	Age Group	Diagnosis & Estimated Amount of Vision	Birth Weight	Length of Gestation, Mo.	Sex	Intelligence Classification	Comments
22		RLF, possible object perception	15 ½ oz.	6	M	IQ 90-109 Hayes-Binet	Is in 1st year in a segregated public school; below-average performance; the impression at the school is that he is bright, but emotionally disturbed
23		RLF, light perception	?	?	M	Mentally retarded	Retardation considered by staff of F. S. B. C. as possibly due to environmental limitation
24		RLF	?	?	M	Mentally retarded	Diagnosed as having "brain damage"
25	5 yr. 9 mo. to 6 yr. 9 mo.	RLF, light perception	2 lb. 8 oz.	6	F	Normal	In segregated residential nursery school with average adjustment; some spasticity
26		RLF	2 lb. 6 oz.	6	M	Normal	Alert child who has been attending sighted kindergarten for the past year
27		RLF, form perception	3 lb. 6 oz.	6	M	Normal	In integrated kindergarten program for past year, with adequate adjustment
28		RLF, some lateral vision	3 lb.	6	F	Normal	In integrated kindergarten, with adequate adjustment
29		RLF, object perception	2 lb. 9 oz	7	F	Normal	Normal development in a good home; good adjustment in regular public school kindergarten; more initiative & social freedom than sighted twin
30		RLF, object perception	2 lb. 15 oz.	6 ½	M	Normal	Had 2 yr. in an integrated nursery school; in 1st year in integrated public kindergarten; average ability, overactive
31		RLF	3 lb. 4 oz.	7	F	Normal	Alert child
32		RLF, light perception	2 lb. 5 ½ oz.	6	F	Normal	In segregated residential nursery school for 1 yr.; satisfactory development; extremely deprived home situation
33		RLF	2 lb. 5 oz.	6	F	Normal	Had 3 yr. experience in an integrated nursery school; now in 1st yr. integrated public school kindergarten; fair adjustment & intelligence estimated above average
34		RLF, light perception	2 lb. 13 oz.	6 ½	M	Mentally retarded	Placed in state hospital for the mentally retarded
35		RLF, totally blind	2 lb. 10 oz.	6 ½	M	Mentally retarded	Placed in state hospital for the mentally retarded
36		RLF	2 lb. 10 oz.	6 ½	F	Mentally retarded	Twin has cerebral palsy
37		RLF	2 lb. 7 oz.	6	F	Mentally retarded	Applicant for state hospital for the mentally retarded
38		RLF	3 lb. 11 oz.	6 ½	M	Normal ?	Till 2 yr. of age very overprotected and isolated; a fearful, disturbed child when first seen by staff of F. S. B. C.; made slow progress in nursery school for sighted children; now has had 1 yr. in integrated kindergarten in a private school; good participation, is well liked, but slow comprehension, especially of abstractions

TABLE 7.—*Case Summaries of Children Blind as a Result of Causes Other Than Retrolental Fibroplasia (RLF)*

Case No.	Age Group	Diagnosis & Estimated Amount of Vision	Birth Weight	Length of Gestation, Mo.	Sex	Intelligence Classification	Comments
39	8 yr. 9 mo. to 9 yr. 9 mo.	Gliomа & iritis following encephalitis		Premature	M	IQ 82	Is in 2d yr. in an integrated public school program; school adjustment is good; is very well liked; has always shown good promise
40		Bilateral retinal detachment: light perception	2 lb. 4 oz.	6	M	IQ 70 Hayes-Binet, mentally retarded?	Had an extremely limited environment during first 4 yr. of life; is now in 2d yr. in segregated public school for the blind; good academic progress, more than satisfactory for intelligence
41		Congenital cataracts, partial right; borderline braille or sight-saving class candidate		Term	M	Normal	Had 1 yr. in general public school kindergarten and 2 yr. in sight-saving and Braille classes; has made a good adjustment in school and does well socially
42		Optic nerve atrophy		Term	M	Mentally retarded	
43		Glaucoma		Term	M	IQ 108	Had 1 yr. in an integrated nursery school and is now in 3d yr. in a residential school for the blind; after initial homesickness became very well adjusted; from a poverty-stricken family
44		Congenital eye defect. Deaf		Term	M	Mentally retarded	In a special school for mentally retarded children
45		Congenital cataracts; form vision only & deaf		Term	F	Mentally retarded	Is in 4th yr. in the deaf-blind division of the state residential school; no IQ has been obtained, appears very slow; "some difficulty in adjustment because of her mother's ambivalent feelings which makes her uncooperative at times"
46		Optic nerve atrophy & question of brain damage; no central vision		Term	M	IQ 78	At age 4 ½ yr. recommended for state institution for mentally retarded; instead, placed by parents in special private school; now is in 3d grade sight-saving classes in segregated public school for the blind; mental potential considered to be higher than recorded IQ; although has initially considered "blind," visual efficiency has increased tremendously.
47	7 yr. 9 mo to 8 yr. 9 mo.	Optic nerve atrophy		Term	M	Mentally retarded	Developed cerebral palsy as well as optic nerve atrophy following an accident in infancy
48		Optic nerve atrophy		Term	M	Mentally retarded	
49	6 yr. 9 mo. to 7 yr 9 mo.	Severe myopia	8 lb. 5 oz.	Term	M	Normal	Is in the 1st grade of a segregated school for the blind and is learning Braille; receives C grades
50		Optic nerve atrophy (?)	2 lb. 6 oz.	6	F	IQ 101, W.I.S.C.*	Had a yr. of integrated public school kindergarten and is now in integrated 1st grade and is learning Braille; has made a good school adjustment; it is felt that her potential is greater than the recorded test results would indicate
51		Cataracts	7 lb.	Term	M	Normal	Good adjustment in kindergarten for sighted children

* W. I. S. C. Wechsler Intelligence Scale for Children.

TABLE 7.—*Case Summaries of Children Blind As a Result of Causes Other Than Retrolental Fibroplasia (RLF)*—Continued

Case No.	Age Group	Diagnosis & Estimated Amount of Vision	Birth Weight	Length of Gestation, Mo.	Sex	Intelligence Classification	Comments
52	6 yr. 9 mo. to 7 yr. 9 mo.	Microphthalmos		Term	M	Normal ?	The early impressions of the staff at the F. S. B. C.† were that this child's development was slow and that he was possibly retarded; the pediatrician disagreed; child had 2 yr. in an integrated nursery school, but progress was not reported; he is now in a segregated public school for the blind; his adjustment is reported as satisfactory there
53		Retinoblastoma	6 lb.	Term	F	IQ 96	Is in 1st yr. in a residential school for the blind & has made a good school adjustment
54		Optic nerve atrophy		Term	F	Mentally retarded	Optic nerve atrophy followed meningitis at age 2 wk.
55		Optic nerve atrophy		Term	M	Mentally retarded	Is in a state institution for the mentally retarded
56	5 yr. 9 mo to 6 yr. 9 mo.	Optic nerve atrophy		Term	F	Normal	Optic nerve atrophy followed encephalitis; is subject to convulsions & rages & is emotionally disturbed; however, is in an integrated public school kindergarten & is considered to have average intelligence
57		Microphthalmos; left eye: total blindness; right eye: severe myopia	2 lb. 10 oz.	6½	M	Normal	Is in an integrated public school kindergarten; has made an excellent adjustment & is considered a capable child
58		Retinoblastoma		Term	F	IQ 132	Is in her 1st year in an integrated kindergarten & has made an average adjustment; the parents are considered to be very overprotective
59		Congenital retinal fold; peripheral vision	2 lb. 12 oz.	6½	M	Normal	Has made a satisfactory adjustment in an integrated public school kindergarden & previous developmental progress had been good; rather tense child; parental overexpectations
60		Optic nerve atrophy and hydrocephalus		Term	F	Mentally retarded	In state hospital for the mentally retarded

† F. S. B. C., Field Service for Preschool Blind Children.

owing to emotional disturbance or environmental deprivation. It is well known that such pseudoretardation can readily occur in blind children.[19,20] It was for this reason that only cases known to the Field Service for blind preschool children were included. It was hoped that through the services rendered to the parents of these children in the preschool period the incidence of emotional and environmental retardation might be minimized. Thus, a truer picture of the problem of retardation among the blind might be obtained. It soon became apparent, however, that many parents did not seek help from this agency until the children were nearly of school age and that some who came for the agency service could not really accept the help offered. Nevertheless, as the protocols will indicate, many parents and children did receive profitable help from this agency that enriched the emotional and perceptual environment of the blind child and helped him achieve his full potential.

This study did bring about the realization that there are significantly larger numbers of blind children who are mentally retarded and have neurological disorders than is recorded in the general population. It would also seem fair to say that loss of visual perception is not a significant cause of mental retardation, since the majority of the blind children have average or better than average intelligence.[3] One would then want to consider the possibility that some causes of blindness may also be significant causes of mental retardation and neurological disorders.

Though it is now fairly well demonstrated that the premature infant who has received no insults to his nervous system such as hemorrhage or anoxic episodes can have normal mental development,[9,13,21-23] it is also known that the incidence of neurological disorders and mental retardation occur with greater frequency among premature infants than in the general population.[9-12,21,22] For this reason, one might expect a somewhat greater incidence of mental retardation and neurological disorders among children with blindness due to retrolental fibroplasia than in the general population, since retrolental fibroplasia occurs almost exclusively among premature infants. Furthermore, some have seriously considered the possibility that the high oxygen concentrations that cause retrolental fibroplasia may also cause cerebral damage.[8,17,18]

Initially it was thought that a comparison of the mental development of premature infants with blindness due to retrolental fibroplasia with a group of full-term infants with blindness due to other causes might reveal some evidence that prematurity and oxygen poisoning are significant factors in the incidence of mental retardation and neurological disorders in children blind as a result of retrolental fibroplasia. As previously indicated, this study did not reveal such a difference.

Norris[2] reports 5% of 209 children blind as a result of retrolental fibroplasia as "retarded," whereas 14% of 86 children blind as a result of other causes were considered "retarded." She indicated that this might be explained by the fact that 40% of this group of children had associated physical handicaps, whereas only 10% of the children blind as a result of retrolental fibroplasia had associated physical handicaps. When the children with associated physical handicaps were removed from both groups, there was no difference in the incidence of mental retardation between the groups. It was from 3% to 5% for both. This would seem to indicate at least that children blind as a result of retrolental fibroplasia have no greater incidence of mental retardation than children blind as a result of other causes. Norris came to the following conclusion: "There is no evidence that retrolental fibroplasia is associated with either a specific or a generalized brain defect. When a child with retrolental fibroplasia is retarded in his functioning and there are no specific neurological findings, the retardation must be presumed to be directly related to complex social and environmental factors."

Hayes,[3] working at the Perkins Institute for the Blind, has tested many blind children and adults and has developed the Interim Hayes-Binet test. He reports that when 501 children blind from any cause were tested, the incidence of mentally defectives (IQ of 70 down) was 10.6%, as compared with 2.2% of 2904 sighted children reported by Terman. This accumulation of defectives, he indicates, could be explained as a result of the admission to the Perkins Institute of children of doubtful ability, often handicapped in their development by restriction of activity, by parental oversolicitude or lack of basal security, and by the presence of additional handicaps, such as hearing loss or cerebral palsy. In comparing 65 children blind as a result of retrolental fibroplasia and 141 children blind as a result of other causes, using the Interim Hayes-Binet test, he found similar distributions of scores in the

two groups, with 12.4% and 12.8% in the mentally defective range, respectively.

Hayes has repeated these findings in some unpublished data [4] with much larger samples, including children in several schools beside Perkins Institute. The percentage of mentally defective children ranges from 7% to 17% in the various schools and is the same for blindness due to retrolental fibroplasia and that due to other causes. Of particular importance is the fact that the remainder of the scores follow a distribution very similar to that for sighted children, with comparable percentages of children in high-average, superior, and very superior categories.

Knobloch [10] studied 57 premature infants with birth weights of 1500 gm. or less, all with normal vision. These children were given neurological examinations and Gesell tests at 40 weeks of age. She reported 12.3% as showing overt neurological defects and a similar percentage as mentally defective on Gesell testing. The per cent with overt neurological defects and mentally defective corresponds with the incidence of mental deficiency as reported by Hayes for children with blindness due to retrolental fibroplasia. This is of interest because the majority of children blind as a result of retrolental fibroplasia have birth weights of 1500 gm. or less.

Blegen,[22] reporting on 476 prematurely born children of school age, found 4.6% with IQ's less than 70. She included all birth weight groups up to 2500 gm. Alm,[9] reporting on 999 prematurely born boys and 1002 full-term controls, all 20 years of age and over at the time of study, found that 3.3% of single-born premature infants and 5.8% of pleural-born premature infants had attended special classes, as compared with 1.7% of the full-term controls. This study included all premature birth weight groups under 2500 gm. and, in fact, included only 21 subjects with birth weights less than 1500 gm., in contrast to 803 with birth weights over 2000 gm. Thus, even though this study was heavily weighted for the larger premature infants, the incidence of mental defect was at least twice that of the full-term control group.

The studies demonstrating that the incidence of mental defectiveness was no greater in children blind as a result of retrolental fibroplasia than among children blind as a result of other causes might be interpreted as indicating that prematurity is not a contributing factor. The studies cited above relative to prematurely born children as a group would suggest that the mental and neurological complications of prematurity are a significant factor. If this is so, then there must be factors other than prematurity that cause mental retardation and neurological disorders in the groups with blindness "due to other causes," since most of these children are born at term. In this study only 5 of the 22 cases with blindness "due to other causes" were premature. As indicated in Table 5, the group considered to have blindness due to other causes is very heterogeneous. Some of the diagnoses, such as optic atrophy, are known to be frequently associated with neurological problems and mental deficiency. Cordes [24] reports that, exclusive of the cases of traumatic origin, 35% of 43 cases of primary optic atrophy showed mental deficiency. Mungovan [5] took this into consideration in his study of blindness due to retrolental fibroplasia and blindness due to other causes. He listed those cases of blindness due to optic atrophy separately and found that 55% of 29 children with this diagnosis were considered retarded, as compared with 18.8% of 186 children blind as a result of retrolental fibroplasia. His group of 53 cases of blindness due to other causes excluding optic atrophy had an incidence of mental retardation of 37.7%.

It is probable that the "other causes" category should be broken down into many subgroups before any significant comparisons of mental development of blind children can be made. Even optic atrophy is an all-inclusive diagnosis for many etiological conditions, as Cordes' [21] analysis of 88

cases indicates. Congenital cataracts have multiple causes. Congenital cataracts occurring in an infant after the mother has had rubella in the first trimester are often associated with other anomalies, including neurological problems and mental deficiency, whereas congenital cataracts due to other causes may not be associated with other anomalies. A study of children who are blind as a result of enucliation done for retroblastoma might be very revealing. It is possible that these children as a group might have a lower incidence of neurological problems and mental deficiency than children blind as a result of other causes.

The major questions still remain unanswered by the studies done to date. One could assume that the higher incidence of mental retardation among blind children than that in the sighted population is primarily environmental in origin, due to perceptual deprivation and emotional problems. This might be indicated by the fact that the incidence of mental retardation is the same in children with blindness due to retrolental fibroplasia and with blindness due to other causes. Also, those who work with blind children see many children who have been deprived of almost any opportunity to learn and others who have been sufficiently emotionally disturbed to function in a retarded manner.[18,19] One would not want to overlook these children.

On the other hand, there is evidence that premature infants who are not blind have a higher incidence of neurological problems and mental deficiency than full-term infants, and it is important to know whether oxygen poisoning, which is accepted as the cause of retrolental fibroplasia, also increases the incidence of neurological disorders in premature infants. Certainly, comparing such a heterogeneous group as those with "other causes of blindness" with children blind as a result of retrolental fibroplasia would not seem to be an adequate approach.

This study does not answer these major questions, but it does indicate the need for more detailed studies of more homogeneous groups of blind children; otherwise the answers to the questions we are asking will remain obscure.

Summary

This study was undertaken in an effort to determine the possible mentally retarding effects of prematurity and/or oxygen poisoning on children with blindness due to retrolental fibroplasia. The incidence of mental retardation among 38 children with blindness due to retrolental fibroplasia is compared with the incidence among 22 children with blindness due to other causes. Only children of school age between 5 years 9 months and 9 years 9 months were studied, so that school progress and test results could be used to aid in evaluating the mental abilities of these children. Furthermore, only cases known to the Field Service for blind preschool children were considered, so that the possibilities of pseudo or environmental retardation might be minimized.

Any child with a reported IQ of less than 70 was considered mentally retarded. Those children with reported IQ test results were judged on the basis of school reports and on the observations of the worker for the Field Service for blind preschool children.

Of the 38 children blind as a result of retrolental fibroplasia, 12, or 32%, were considered mentally retarded. Similarly, of the 22 children blind as a result of other causes 9, or 41%, were classified as mentally retarded. The difference between the two groups was not considered statistically significant.

Analysis of the two groups did not significantly alter the numerical findings, but it suggested various difficulties and possible fallacies in this type of comparison. First of all, despite efforts to minimize the factor of emotional and environmental retardation, this possibility would need to be considered in at least three, or one-quarter of the children considered retarded and blind as a

result of retrolental fibroplasia. Furthermore, analysis of the group of children blind as a result of other causes revealed it to be a very heterogeneous group. Within this group the children with blindness due to optic atrophy accounted for two-thirds of the cases of mental retardation. It is questionable whether one can use such a heterogeneous group such as those blind as a result of other causes in comparative studies, as is commonly done.

Some of the pertinent literature is reviewed. The consensus of opinion seems to be that premature birth with absolutely no complications does not contribute to an increased incidence of mental retardation. On the other hand, premature birth is accompanied by many hazards and complications, and so the neurological sequelae and associated mental retardation are increased in these children over those of the general population. Whether oxygen poisoning contributes to additional neurological complications and associated mental retardation or not in children with blindness due to retrolental fibroplasia remains unanswered.

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Studies of 17-Hydroxycorticosteroids

XIV. Plasma 17-Hydroxycorticosteroid Concentrations at Death in Human Subjects

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Markedly elevated circulating concentrations of 17-hydroxycorticosteriods (17-OHCS) have been found by a number of workers[1-6] in patients with terminal illnesses. However, little is known concerning factors which may influence responsiveness of the pituitary-adrenal system to impending death. The purpose of this communication is to present observations concerning the relationship of such factors as age, chronicity of illness, nature of the disease process, mode of death, and previous corticoid therapy to plasma concentrations of 17-OHCS at death in human subjects.

Methods

Sixty-four patients ranging in age from ½ hour to 90 years were utilized in this study. The newborn infants were full-term, except as indicated in Table 1. Blood samples were obtained by cardiac puncture, usually within 5 minutes and in all cases within 20 minutes after death. In addition, serial blood specimens were obtained prior to death from six patients with craniocerebral trauma. Plasmas were separated by centrifugation and stored in deep-freeze refrigerators until used for analyses. Plasma concentrations of free (nonconjugated) 17-OHCS were determined by the method of Nelson and Samuels[7] as modified by Eik-Nes, Nelson, and Samuels.[8]

Observations

Table 1 presents individual data concerning age, sex, diagnosis, nature and duration of terminal episode, and levels of 17-OHCS found in plasma specimens obtained immediately after death in 37 patients who died of a variety of illnesses. An additional 27 patients who had extensive adrenal or intracranial lesions or who received adrenocortical hormones prior to death will be considered separately, in Tables 3 through 6. For purposes of comparison, normal plasma 17-OHCS values obtained in this laboratory are presented in Table 2.

Influence of Age.—The relationship of age to the postmortem plasma 17-OHCS concentration is summarized graphically in Figure 1. Eight patients in the age group ½ hour to 3 days had a mean plasma 17-OHCS concentration of 31 ± 8.1 * μg. per 100 ml. The mean plasma 17-OHCS concentration (micrograms per 100 ml.) was 70 ± 9.2 in the 17-day to 9-year group (18 patients), 77 ± 16.7 in the 38- to 69-year group (6 patients), and 90 ± 15.9 in the 72- to 86-year group (7 patients). Statistically, the mean value for the infants under 3 days of age is significantly lower ($P < 0.01$) than the mean for patients of the next older age group or for all older patients combined; no significant differences exist among the mean values for the three older age groups.

Acute vs. Chronic Illness.—Figure 1 illustrates the relationship of chronicity of illness to the postmortem plasma concentration of 17-OHCS in patients over 2 months of age. Among those patients in whom death was preceded by chronic illness and debilitation, the mean postmortem plasma 17-OHCS concentration was

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* Standard error of the mean (S. E. M.).

TABLE 1.—*Postmortem Plasma 17-OHCS Concentrations*

Patient	Age	Sex	Diagnosis	Terminal Episode		Postmortem Plasma 17-OHCS, μg/100 Ml. *
				Nature	Approx. Duration	
1	½ hr.	M	Hydrops fetalis; prematurity (31 wk. gestation)		------	6
2	6 hr.	M	Multiple congenital anomalies	Pulm. atelectasis	6 hr.	10
3	11 hr.	M.	Prematurity (1760 gm.) Fetal atelectasis		------	49
4	1 day	M	Prematurity (1700 gm.) Ruptured liver with i. p. hemorrhage	Shock	10 hr.	23
5	1 day	F	Pulm. hyaline membrane, atelectasis	Atelectasis	1 day	31
6	2 days	M	CHD †: IVSD, aortic atresia, PDA	Congest. failure	1½ days	29
7	3 days	M	Erythroblastosis fetalis	Exchange transf., congest. failure	4 hr.	22
8	3 days	F	CHD: aortic atresia, PDA, IVSD	Congest. failure	1 day	77
9	17 days	M	CHD: coarct. aorta, PDA; acute bronchitis, 7 days	Pulm. atelectasis	2 days	25
10	18 days	M	Pseudomonas septicemia		2 days	134
11	63 days	M	CHD: aortic atresia, PDA	Congest. failure	3 wk.	61
12	68 days	M	Staphylococcal sepsis	Same ‡	2 mo.	54
13	4 mo.	M	CHD: coarct. aorta, patent foramen ovale	Pulm. edema	1 hr.	66
14	5½ mo.	F	CHD : ? truncus arteriosus	Pulm. edema ‡	7 hr.	72
15	7 mo.	M	Progressive spinal musc. atrophy	Resp. paralysis	3 days	109
16	7 mo.	F	CHD: tetralogy of Fallot	Pneumonia	1 day	130
17	9 mo.	F	Gaucher's disease	Pneumonia	2 days	46
18	18 mo.	F	Diabetic acidosis		1 wk.	69
19	2 yr.	M	Parathion poisoning		20 hr.	51
20	3 yr.	M	Reticuloendotheliosis, 4 yr.	Sudden, ? cardiac decomp.		131
21	5 yr.	F	Acute leukemia	?		84
22	7 yr.	M	Hodgkin's disease, 1½ yr.	Congest. failure	2 days	28
23	9 yr.	M	Acute leukemia	Intest. hemorr., shock ‡	10 min.	89
24	9 yr.	M	Mucoviscidosis, cor pulmonale, debilitation	Congest. failure	2 mo.	7
25	38 yr.	M	Mult. pulm. emboli, remote & recent; debilitation	Pulm. embolism	2 hr.	63
26	53 yr.	M	Postgastrectomy perforation, peritonitis	Peritonitis, septicemia	18 days	40
27	54 yr.	M	Silicosis, chronic cor pulmonale	Congest. failure (inc. severity 1 wk.)	1 yr.	36
28	56 yr.	M	Perfor. duod. ulcer; peritonitis	Shock ‡	1 day	129
29	67 yr.	F	Arteriosclerotic, CV dis.	Ventr. fibrillation	20 min.	126
30	69 yr.	M	Myocardial infarct, 3 hr.	Pulm. edema ‡	3 hr.	63
31	72 yr.	M	Arteriosclerotic CV dis., pneumonia	Pulm. edema ‡	5 hr.	148
32	74 yr.	F	Gen. abd. carcinomatosis	Intest. obstruct. ‡	2 days	49
33	76 yr.	F	Rectal carcinoma, perfor. cecum, peritonitis, 2-3 wk.	Resp. obstruct., dehydration	Acute	36
34	79 yr.	F	Myocardial infarct.	Cardiac rupture, tamponade	?	109
35	80 yr.	F	Hypertensive CV dis.; severe, prolonged inanition	Pneumonia	9 days	70
36	82 yr.	M	Acute bact. endocarditis		3 days	135
37	86 yr.	M	Myocardial infarct		?	78

* Normal mean values are given in Table 2.

† CHD, congenital heart disease; IVSD, interventricular septal defect; PDA, patent ductus arteriosus.

‡ Autopsy not performed; "diagnosis" and "terminal episode" based on clinical impression. In all others these were verified by postmortem examination. Except where indicated otherwise, routine gross and microscopic examination of pituitary and adrenal glands of autopsied patients revealed no abnormalities except for depletion of adrenocortical lipid in some instances.

59±7.2μg/100 ml. (range, 7μg. to 131μg.), as compared with a mean value of 101± 10.4μg/100 ml. (range, 51μg. to 148μg.) in those who enjoyed comparative good health prior to the onset of their acute terminal illnesses. Mean values for these groups differ significantly ($P<0.01$). The lowest plasma 17-OHCS concentration of the

TABLE 2.—*Mean Values for 17-OHCS Found in This Laboratory in Normal Persons*

Group	Determinations, No.	Plasma 17-OHCS, μg/100 Ml. Mean	S. E. M.	Range
Newborn (1-4 days)	14	12 *	±1.5	1-23
Children	40	12	±1.3	0-27
Adults	160 †	11	±0.5	0-28

* 17-Hydroxycorticosterone by a modification of the method of Sweat. [10, 11] All other determinations were done by method of Nelson and Samuels. In this laboratory, close agreement has been found between these methods. [12]

† Represents 45 persons from whom samples were obtained at varying hours during day and night.

acute illness group was in a 2-year-old child who died from parathion poisoning. The possible influence of this type of poisoning on pituitary-adrenal function is unknown.

Fulminating Encephalopathies.—Table 3 presents data from 15 patients with fatal craniocerebral trauma, 2 with purulent meningitis, and 1 who died as the result of a rapidly expanding intracranial neoplasm. These persons are considered separately since with respect to plasma 17-OHCS concentrations at death they seemed to differ, as a group, from patients who died of other causes: Elevated levels were found only in 7 of these patients, the remaining 11 patients having plasma 17-OHCS values of 13μg/100 ml. or less. Four persons of this group had no measurable 17-OHCS in their plasmas at death.

Figure 1 graphically presents the data from patients of this group and compares these values with those obtained from patients who died with other acute and chronic illnesses. The mean plasma 17-OHCS concentration at death in the patients with fulminating encephalopathies (21±4.2μg. per 100 ml.) is significantly lower ($P<0.01$) than the means for the groups of patients who died following acute (101±10.4μg. per 100 ml.) or chronic (59±7.2μg/100 ml.) illness and for the latter two groups combined (75±7.1μg/100 ml.). Indeed, only two patients of this group had plasma 17-OHCS concentrations which were even as high as the lowest value obtained in patients who died of other acute illnesses, and both of these persons had peritonitis in addition to craniocerebral injuries (Patients 45 and 48).

There was no consistent correlation between 17-OHCS concentrations at death and the duration of illness or the presence or absence of associated injuries among the patients with craniocerebral trauma (Table 3). However, the individual steroid data did correlate to some extent with severity of encephalopathy as evidenced by certain clinical manifestations. Eleven patients exhibited prolonged hypotension, hypothermia, or apnea (or a combination of these); the highest postmortem plasma 17-OHCS concentration among these persons was 13μg/100 ml. (mean, 6μg.). Among the seven patients who presented none of these signs except, perhaps, for brief periods immediately prior to death, 17-OHCS values ranged from 24μg. to 65μg/100 ml. (mean, 45μg.).

Serial Measurements of Plasma 17-OHCS Concentrations.—Serial measurements were made in six of the patients with fatal craniocerebral trauma; these data are shown in Figure 2 in relationship to the clinical course. Plasma samples obtained during the first two to three hours

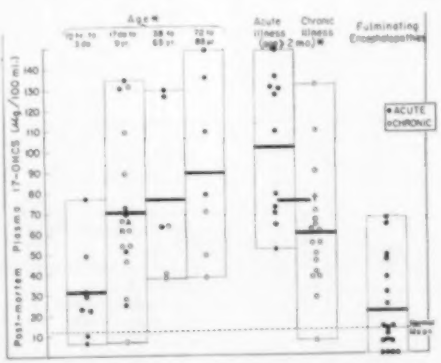

Fig. 1.—Plasma 17-OHCS concentrations at death. The asterisk indicates that patients with fulminating encephalopathies, destructive adrenal lesions, and those recently treated with corticoids are excluded. *A*, Patient 56, anencephalic; *H*, Patient 57, hydranencephalic; + indicates the mean of the acute plus chronic illness groups.

TABLE 3.—*Plasma 17-OHCS Concentrations at Death in Patients with Fulminating Encephalopathies*

Patient	Age	Sex	Manifestations	Duration, Hr.	Anatomical Findings *	Postmortem Plasma 17-OHCS, μg/100 Ml.
			Craniocerebral Trauma			
38	19 yr.	M	Coma since injury, pneumothorax	1	Multiple skull fractures †	37
39	51 yr.	M	Coma since injury, apnea.	3	†	12
40	6 mo.	M	Coma since injury, convulsions, fractured femur	4½	Multiple skull fractures, extensive subdural hemorrhage	30
41	90 yr.	M	Coma since injury, hypotension, fractures of ribs & radius	4½	Craniotomy: mod. subdural hemorrhage †	7
42‡	15 yr.	M	Coma since injury, hypotension, multiple limb fractures, pneumothorax	15	Extensive frontal fractures with extrusion of cerebral tissue †	13
43‡	76 yr.	M	Coma since injury, irregular respiration, fractured femur	24	Multiple cerebral lacer., subdural hematoma, maceration post. rt. frontal cortex, hemorr. left occip. cortex & putamen	24
44	3 yr.	M	Coma since injury, apnea, hypotension, severe hypothermia	24	Basilar skull fracture, cerebral edema	6
45‡	5 yr.	F	Coma since injury, convulsions, rupture of gastric ulcer, fever (104 F)	25	Multiple skull fractures, maceration rt. frontal & parietal cortex, small sub- and extradural hemorrhages	65
46	3 yr.	F	Coma since injury, apnea, hypotension, severe hypothermia	25	Craniotomy: Multiple cerebral lacer. †	0
47	4 yr.	F	Brief unconsciousness after minor fall; lucid thereafter; sudden, unexpected death (alert 15 min. earlier)	37	Extensive temporoparietal fracture; cerebral edema; multiple focal cortical ecchymoses (front., par., occip., temp.); cerebral edema	48
48‡	7 yr.	M	Coma since injury, convulsions, traumatic perforation of stomach, fever (105 F)	43	Basilar skull fractures, contusion left frontal cortex, extensive sub- and extradural hemorrhages	63
49‡	20 yr.	M	Coma since injury, apnea	44	Bullet wound penetrating rt. frontal to rt. occipital; subdural hemorrhage; adenohypophysis: small area of necrosis	6
50‡	15 yr.	M	Coma since injury, apena, hypotension, fever (102 F)	91	Basilar skull fracture, extensive subdural hemorrhage, cerebral edema, sm. subarach. hemorr. rt. frontal cortex	13
51	2 yr.	M	Unconscious immed.; briefly lucid, then coma followed by apnea; severe hypothermia, hypotension	94	Craniotomy: cerebral edema, diffuse subdural hemorrhage †	0
52	51 yr.	M	Coma first 24 hr., disoriented for 24 hr., then coma to death; fever (102 F)	108	Depressed parietal fracture, multiple cerebral lacerations	46
			Meningitis			
53	15 days	M	Coma, convulsions, shock, apnea, fever (102-105 F)	48	Meningitis, purulent (Staph.)	0
54	18 days	M	Coma, convulsions, shock, apnea, fever (103 F)	48	Meningitis, purulent (E. coli); Mongolism	0
			Rapidly Expanding Intracranial Neoplasm			

TABLE 3.—*Plasma 17-OHCS Concentrations at Death in Patients with Fulminating Encephalopathies*—Continued

Patient	Age	Sex	Manifestations	Duration, Hr.	Anatomical Findings*	Postmortem Plasma 17-OHCS, μg/100 Ml.
55	37 yr.	F	Progressive symptoms, 3 wk.; papilledema, 1 wk.;		Glioblastoma multiforme, left angular gyrus;	10
			coma,	24	cerebral edema	
			apnea,	20		
			hypotension, hypothermia	6		

* Except where indicated otherwise, routine gross and microscopic examinations of pituitary and adrenal glands of autopsied patients revealed no abnormalities except for depletion of adrenocortical lipid in some instances.

† Autopsy not performed.

‡ Serial studies are shown in Figure 2.

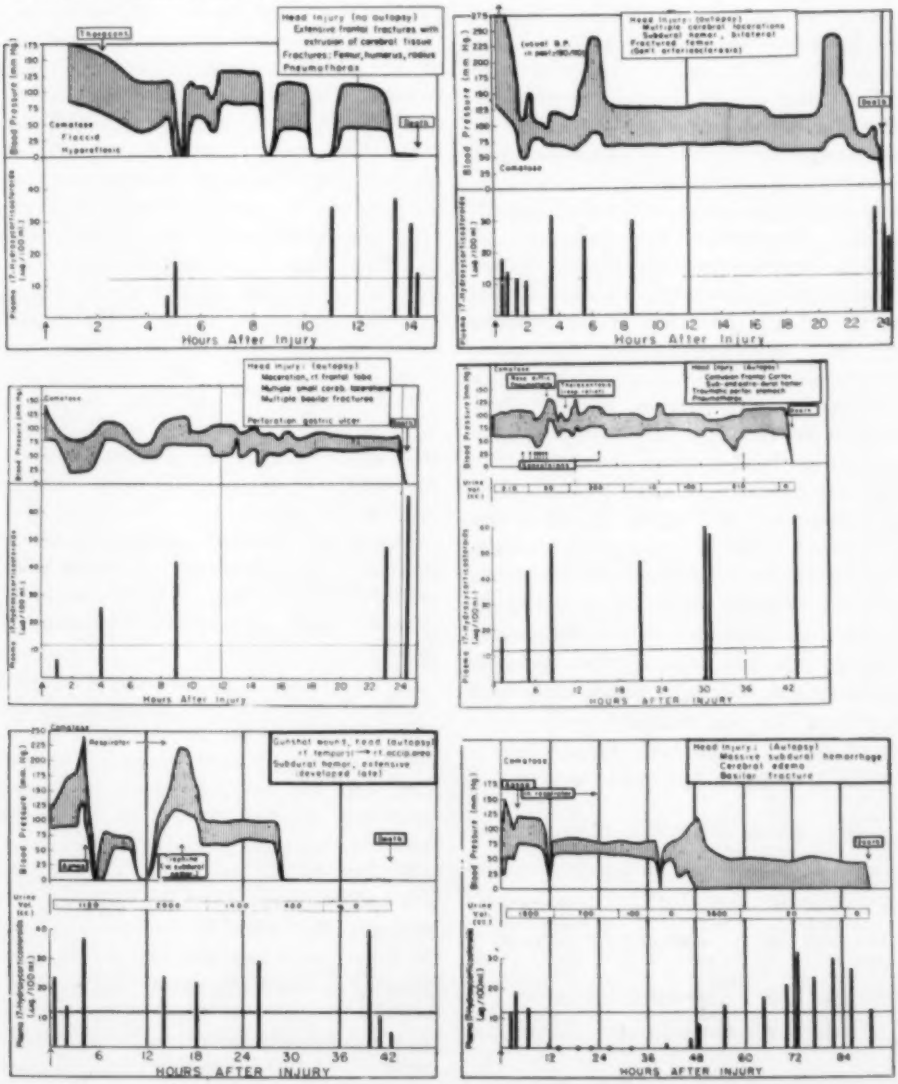

Fig. 2.—Serial measurements of plasma 17-OHCS in patients with fatal craniocerebral trauma. Upper left, Patient 42; upper right, Patient 43; center left, Patient 45; center right, Patient 48; lower left, Patient 49; lower right, Patient 50.

following injury contained 17-OHCS in concentrations which were within the range of resting values seen in normal persons, despite the fact that each of these patients appeared to be in extremis at the time. Patient 50 (lower right, Fig. 2) had no measurable plasma 17-OHCS in the interval between the 14th and 32d hours after injury and did not display definitely elevated 17-OHCS levels until 73 hours after injury. In each of the patients studied serially some elevation of the 17-OHCS level occurred eventually. In certain instances elevations in 17-OHCS concentrations appeared to coincide with the development of oliguria or anuria and may have been related, in part at least, to accumulation of steroid secondary to failure of urinary excretion. The pattern of 17-OHCS concentrations appeared to follow either of two courses: In Patients 45 and 48 (center, Fig. 2) elevations in circulating 17-OHCS concentrations occurred within four hours, persisted throughout the course, and were present at death. Both of these persons had peritonitis secondary to gastric perforation in addition to their craniocerebral injuries. In Patient 45 an ulcer, presumably of the Cushing type, had perforated; Patient 48 suffered a traumatic rupture of the stomach. In the other four subjects (Patients 42, 43, 49, and 50) elevations of circulating 17-OHCS concentrations eventually appeared but were less striking and, in each instance, declined rapidly at the time of death.

Absence of Cerebral Hemispheres.—Table 4 presents data from two patients who exhibited complete absence of cerebral hemispheres.

TABLE 4.—*Plasma 17-OHCS at Death in Patients with Absent Cerebral Hemispheres*

Patient	Age, Days	Sex	Diagnosis *	Postmortem Plasma 17-OHCS, μg/100 Ml.
56	17	F	Anencephaly (adrenals present)	66
57	75	F	Hydranencephaly (terminal pneumonia)	60

* See text for more detailed description.

Patient 56 was an anencephalic infant who died at the age of 17 days. The midbrain, brain stem, and pituitary were grossly intact. Adrenal glands were present but small, having a combined weight of 1.4 gm. The plasma 17-OHCS concentration at death was 66μg/100 ml. (Details concerning this infant and studies of her adrenal function will be presented elsewhere.)

Patient 57 died of pneumonia at the age of 75 days. Necropsy revealed virtually complete absence of cerebral hemispheres: Only the most anterior portion of the frontal lobe and the posterior portion of the occipital lobe could be recognized as brain tissue, the remainder being made up of a thin, membranous sac of fluid. The midbrain, brain stem, and pituitary were grossly intact. The adrenal glands had a combined weight of 10 gm. The plasma 17-OHCS concentration at death was 60μg/100 ml.

It can be seen in Figure 1 that the plasma 17-OHCS levels in these patients were comparable to those seen at death in infants of comparable age in whom cerebral hemispheres were intact.

Destructive Adrenal Lesions.—Table 5 presents data concerning postmortem plasma 17-OHCS concentrations in four patients with destructive adrenocortical lesions.

Patient 58, an 87-year-old woman, seemed mildly ill with bronchopneumonia, but she died suddenly on the fourth day of illness after unexpected cardiovascular collapse. Her skin was not pigmented. Ten years previously she had noted a 25 lb. weight loss and weakness which persisted for one year, but she did well subsequently except for a slight progressive loss of memory. At necropsy her adrenals showed extensive necrosis; numerous acid-fast bacilli were present. A single area constituting approximately one-tenth the mass of one adrenal was recognizable histologically as adrenal cortex, and this showed marked mononuclear infiltration. A plasma specimen ob-

TABLE 5.—*Plasma 17-OHCS at Death in Patients with Known or Suspected Destructive Adrenal Lesions*

Patient	Age	Sex	Diagnosis	Adrenal Pathology	Postmortem Plasma 17-OHCS, μg/100 Ml.
58	83 yr.	F	Addison's disease	Extensive necrosis (minute area intact)	10
59	9 yr.	F	Meningococcemia; "Waterhouse—Friderichsen syndrome" ?	No autopsy	7
60	13 mo.	M	Bilateral renal vein thrombosis	Complete necrosis of 1 gland; other appeared normal	0
61	70 yr.	F	Carcinoma of gallbladder, metastatic	Extensive tumor infiltration; thrombosis of central vein	8

tained immediately after death contained 17-OHCS in concentration of 10μg/100 ml.

Patient 59, a 9-year-old girl, had fulminant meningococcemia and had been ill for 40 hours prior to death. Cardiovascular collapse developed suddenly two hours prior to death, at which time she was given adrenocortical extract intravenously in a dose of 7 ml. A plasma specimen obtained immediately after death contained 17-OHCS in a concentration of 7μg/100 ml. Permission for autopsy was denied.

Patient 60, a 13-month-old boy, had thromboses of the inferior vena cava and both renal veins. At necropsy one adrenal was found to be completely necrotic; the other was not remarkable. No 17-OHCS could be detected in a plasma specimen obtained immediately after death.

Patient 61, a 70-year-old woman, had carcinoma of the gallbladder with widespread metastases. At necropsy both adrenal glands showed marked infiltration with tumor. The plasma 17-OHCS concentration at death was 8μg/100 ml.

Influence of Previous Corticosteroid Therapy.—Table 6 presents data from three patients, each with acute leukemia, who received varying amounts of hydrocortisone or prednisolone prior to death. In Patient 62 prednisolone was given orally for 30 days, discontinued for 4 days, and then given intravenously over a period of 18 hours, the last dose being administered 8 hours prior to death; no 17-OHCS could be detected in plasma obtained immediately after death. Patient 63 received prednisolone orally for 6 days, the last dose being given 20 hours prior to death; the plasma 17-OHCS concentration at death was 10μg/100 ml. Patient 64 received prednisolone and then hydrocortisone orally over a period of 45 days ending 16 days prior to death; the plasma 17-OHCS concentration at death was 28μg/100 ml.

TABLE 6.—*Plasma 17-OHCS at Death in Patients with Leukemia Recently Treated with Corticoids*

Patient	Age, Yr.	Sex	Duration of Known Disease, Mo.	Hormone Therapy: Drug & Dose	Hormone Therapy: Duration	Interval, Last Dose to Death	Postmortem Plasma 17-OHCS, μg/100 Ml.
62	6	M	15	ΔF * 40 mg. p. o.	30 days	4 days	0
				ΔF 5 mg. i. v.	q. 4 h. × 3	8 hr.	
63	4	M	10	ΔF 30 mg. p. o.	6 days	20 hr.	10
64	5	M	17	ΔF 40 mg. p. o.	20 days		
				F 160 mg. p. o.	19 days	16 da.	28
				Dosage tapered	6 days		

* F, hydrocortisone; ΔF, Δ¹-hydrocortisone (prednisolone).

Comment

The level of 17-OHCS in the plasma at a given moment is the resultant of a number of processes in addition to production. These include degradation, conjugation, excretion, and perhaps others. Thus, considerable caution must be exercised in drawing conclusions with regard to adrenocortical *activity* on the basis of single measurements of free 17-OHCS, even under the most physiologic of circumstances. Such an assessment based on postmortem levels is rendered even more difficult by derangements associated with dying. Indeed, the functional significance of perimortem levels of any constituent of body fluids is open to question. It is possible that terminal fluid compartment changes may have an unpredictable influence on plasma 17-OHCS concentrations. In addition, dying may be associated with pronounced alterations in the processes concerned with disposal of circulating corticoids. Studies of Sandberg et al.[6] have suggested that the elevated 17-OHCS levels in dying patients are due, in part at least, to impaired metabolism of these steroids. With respect to the present studies, any inferences regarding pituitary-adrenal responsiveness are made with reservation and with due recognition of the limitations mentioned above. The finding that virtually all patients, with the exception of those with fulminating encephalopathy or destructive adrenal lesions, and those who received prior treatment with corticoids, had moderate to marked elevations of plasma 17-OHCS concentrations suggests that a *failure* to achieve such an elevation may reflect a failure of pituitary-adrenal response. Additionally, it supports the impression[6] that dying is not associated with adrenocortical exhaustion.

Numerous studies have suggested that there may be a degree of functional immaturity of the pituitary-adrenal system in early infancy; these have been reviewed elsewhere.[13,14] Klein and Rovnanek,[15] however, have reported the finding of a markedly elevated mean 17-OHCS concentration in plasmas from 12 newborn infants following the stress of surgery, fracture, or overwhelming infection, although individual responses were variable. The failure of the very young infants in the present study to develop terminal 17-OHCS elevations of the magnitude seen in older persons might be interpreted as supporting the concept that there is a degree of functional immaturity of the mechanisms responsible for pituitary-adrenal activation in the neonatal period. Since only one group of corticosteroids, the 17,21-dihydroxy-20-ketosteroids, was studied, it is possible that the difference between the findings in infants and in older persons may reflect *qualitative* rather than *quantitative* differences in the adrenocortical secretory response. Other reports have suggested that there are qualitative differences in resting urinary[16-18] and blood[19] corticosteroid patterns between newborn infants and older persons.

That the capacity of the adrenal cortex to respond to stress is not obtunded in elderly persons is suggested, within the limitations mentioned previously, by the observation that their postmortem plasma 17-OHCS concentrations were comparable to those of younger persons.

There is no definitive explanation apparent for the observation that the group of patients who died after chronic, debilitating illness had a lower mean plasma 17-OHCS concentration at death than those who enjoyed comparatively good health prior to the onset of an acute fatal illness. It is possible that a relatively acute death results either in a more intense pituitary-adrenal "stress" response or a greater influence of some extra-adrenal factor or factors which may affect terminal steroid levels. It is possible also that the prolonged stress of chronic illness may result ultimately in some diminution of pituitary-adrenal responsiveness.

The central nervous system is of importance in the regulation of pituitary-adrenal secretion, as indicated by considerable evidence which has been reviewed else-

where.[20,21] There is no definitive explanation for the failure of many of the patients with fulminating encephalopathy to exhibit elevated plasma 17-OHCS levels at death. The possibility that unconsciousness per se was responsible for a relatively deficient terminal steroid response in the patients with fulminating encephalopathy cannot be dismissed from consideration on the basis of the data at hand. In this regard, it has been suggested by Symington et al.[22] that unconsciousness may "protect" the adrenal gland from stress. This suggestion was based on the finding that only those patients who were unconscious prior to death failed to exhibit focal lipid depletion of the adrenal cortex. In addition, it has been reported that barbiturate anesthesia prevents the development of adrenal changes incident to cold stress[23] and inhibits the eosinopenic response to trauma.[24] The production of hematologic changes suggestive of adrenal activation[25] as well as the development of adrenal hypertrophy[26] secondary to electroconvulsive treatments reportedly can be inhibited by anesthesia. Prolonged ether anesthesia has been reported to cause a reduction in circulating levels of corticotropin (ACTH) in adrenalectomized rats.[27] In the present study, a number of patients, either with or without anatomical changes in the central nervous system, developed definitely elevated plasma 17-OHCS levels at death despite the presence of prolonged coma. This is suggestive that factors other than unconsciousness per se may be responsible for the failure of some patients with extensive encephalopathy to develop elevations of plasma 17-OHCS levels at the time of death.

Among patients of the fulminating encephalopathy group, those who failed to develop elevated 17-OHCS levels at death presented the strongest symptomatic evidence of very severe cerebral dysfunction, including prolonged hypotension, hypothermia, or apnea, either singly or in combination. It is suggested, on the basis of these observations, that marked alterations in central nervous system function may result in a failure of the pituitary-adrenal system to respond to the "stress" of dying. The finding of markedly elevated 17-OHCS levels at death in an anencephalic and an hydranencephalic infant suggest that such a response can occur in the absence of cerebral hemispheres, providing that lower centers are present and functioning.

In each of six patients with fatal craniocerebral trauma in whom serial studies were performed, elevated 17-OHCS levels occurred at some time during the hospital course, but in four of these patients 17-OHCS levels declined rapidly at the time of death. It is possible that prolonged hypoxia or inadequate perfusion of the adrenal gland may have resulted in diminished secretion of hormones. In addition, evidence for a decreased rate of corticoid secretion during hypothermia has been reported.[28,29] The possibility of a cause-and-effect relationship between the perimortem decline in steroid levels and the occurrence of death in these patients is open to speculation.

Summary

17-Hydroxycorticosteroid (17-OHCS) concentrations were measured in plasma specimens obtained from 64 human subjects within a few minutes after death. Levels of these steroids were markedly elevated, except under certain circumstances. Newborn infants achieved smaller elevations than older children or adults; no differences with age were apparent beyond the newborn period. Death was accompanied by greater elevations of plasma 17-OHCS levels when it followed acute rather than chronic illness. Four patients with destructive adrenal lesions and three who were recently treated with corticoids failed to develop elevated 17-OHCS levels at death. Among 18 patients with fulminating encephalopathies (15 with head injuries, 2 with meningitis, and 1 with a rapidly expanding brain tumor), the mean plasma 17-OHCS level at death was only 21 μg/100 ml., as compared with a mean value of 101 μg/100 ml. in patients

who died after other acute illnesses. The presence or absence of increased plasma 17-OHCS at death in these persons appeared to be related to the degree of dysfunction of the brain, particularly of subcortical areas. Among the 11 who exhibited prolonged hypotension, hypothermia, or apnea, not a single person had an elevated 17-OHCS level at death. On the other hand, two children without cerebral hemispheres (one with anencephaly and one with hydranencephaly) developed markedly elevated levels.

Doris F. Tippit, Tiona L. Hughes, and Richard B. Young gave technical assistance, and the many house physicians of the Salt Lake County General Hospital assisted in obtaining specimens. Dr. W. T. Bruns, Department of Pediatrics, University of California at Los Angeles, provided the specimen from the anencephalic infant.

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Plasma and Urine Pepsinogen (Uropepsin) Values in Normal Infants and Children

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The present study is concerned with normal values of blood plasma pepsinogen and urine pepsinogen (uropepsin) excretion in infants and children. Recently there has been a revival of interest in this subject, but these investigations have been conducted in the main with normal adults and patients with gastric disturbances and diseases.

Method and Procedure

The study was divided into two parts. One pertained to the determination of blood plasma pepsinogen levels in normal infants and children; the other, to urine pepsinogen (uropepsin) excretion values. Only children free of acute or chronic disease, malignancy, or involvement of the nervous system, as well as allergic, dermatologic, hepatic, metabolic, endocrine, gastrointestinal, cardiopulmonary, hematologic, renal, emotional, or mental disturbance or disease were included in this series. The subjects were obtained at random, as the opportunity presented itself, from private practice, from the outpatient department, or from the inpatient service among those who were admitted to the hospital for corrective or elective surgical procedures. An appreciable number of specimens was obtained from normal children attending a summer camp.

Part I. Blood Plasma Pepsinogen Studies.—Blood plasma pepsinogen determinations were performed with the blood of 62 normal infants and children. The blood was drawn in the morning before breakfast. In 14 subjects of this group, two or three similar blood withdrawals were made on different days. All determinations were done in duplicate. Three to five milliliters of blood was withdrawn. The method used for the determination of pepsinogen in the blood has been described by Mirsky et al.[1] and by Hirschowitz.[2] Standardization of both tyrosine and pepsin was carried out. The tyrosine standard was done as a control for every set of determinations. Among 41 duplicate determinations picked at random, the percentage difference was from 0 to 2.8%. The average was 1.1%.

Part II. Urine Pepsinogen (Uropepsin) Excretion Studies.—This study was divided into three parts.

A. Twenty-four-hour urine collections from 36 normal subjects were obtained, and chemical determinations of the total pepsinogen (uropepsin) content of the urines were made according to the method described by Spiro et al.,[3] Gray et al.,[4] and Grayzel et al.[5] The results are expressed as units of undiluted urine pepsinogen excreted in 24 hours and units excreted per hour (obtained by dividing 24 into the total excreted in 24 hours). Although the urine may stand for three days at room temperature without any significant change in the uropepsin content,[7] nevertheless, in order to avoid a small loss,[8] each large gallon bottle in which the urine was collected contained 5 ml. of 25% sulfuric acid. The children ranged in age from 3 months to 16 years.

B. Twelve-hour, overnight urine collections from 33 normal children, all over 8 years of age, were obtained. No evidence of bed-wetting was observed. Similar procedures were followed in these children as in Group A.

C. Single three- to four-hour urine collections were obtained from 25 normal children, and two to three different single three- to four-hour urine collections were obtained from another group of 21 normal children. These different single urine collections were obtained from the same subjects on the same or different days. The children ranged in age from 5 years to 12 years. All other measures described in Group A were employed here.

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From the Pediatric and Biochemical Departments of the Jewish Hospital of Brooklyn and the Pediatric Department of the State University of New York College of Medicine, Downstate Medical Center. Research Fellows supported by a grant from the Desitin Chemical Company, Providence, R. I. (Mr. Elkan and Drs. Schneck, Garza, and Caviles).

Results and Comments

The results appear in Tables 1, 2, 3, 4, and 5 and are expressed as pepsinogen units percent (P. U. %) in designating the values of blood plasma pepsinogen [2] and as total pepsinogen (uropepsin) units excreted in undiluted urine in 24- and 12-hour urine collections [3] and as pepsinogen (uropepsin) units excreted per hour when referring to urinary values.

The units used in the blood plasma study are the same units as those of Hirschowitz,[2] and so we have a basis of comparison with his results. He defines this unit as follows: "One arbitrary peptic unit (P. U.) is the spectrophotometric equivalent of 1×10^{-4} meq. of L-tyrosine (0.0181 mg.) released in a standard hemoglobin assay in ten minutes." [2] P. U. % represents pepsinogen units in 100 ml.

The urine results are expressed as pepsinogen or uropepsin excreted as units where a unit of activity of uropepsin is defined as the amount releasing 0.04 mg. of tyrosine-like substances in the urine during a 30-minute incubation at 37 C in the standard assay.[3,4]

Sixty-two normal infants and children varied in age from 2 months to 16 years (Table 1). The values in the blood plasma ranged from 10.5 P. U. % to 30.8 P. U. %, with a mean of 21.4 P. U. % and a standard deviation of ±4.12 P. U. %.

In the case of 14 of the normal children (Table 2) where more than one blood analysis for pepsinogen was done on each child on different days but within a period of three days to six weeks, the percentage difference was no greater than 30%, with an average difference of 14.2%. All values were within the normal range, with an average of 20.1 P. U. % and a standard deviation of ±2.7 P. U. %.

Part II. Urine Pepsinogen (Uropepsin) Studies.—A. With the exception of one infant 3 months of age, the ages of the others were from 1½ years to 16 years. In this group of 37 normal subjects, the 24-hour uropepsin excretion ranged from 900 to

TABLE 1.—*Normal Blood Plasma Pepsinogen Levels in Infants and Children*

Case	Age	Sex	Blood Plasma Pepsinogen Units (P. U. %)
1	8 yr.	M	10.5
2	2½ yr.	M	12.1
3	5 yr.	F	14.6
4	12 yr.	F	14.9
5	9 yr.	M	15.4
6	8 mo.	F	15.4 *
7	3 yr.	M	16.3
8	2 yr.	M	16.5
9	1 yr.	F	16.7 *
10	10 yr.	M	16.7 *
11	7 yr.	F	16.7
12	7 yr.	F	17.5
13	5 yr.	M	17.6
14	3 yr.	M	18.0
15	12½ yr.	F	18.3
16	3 mo.	M	18.3
17	11 yr.	F	18.6 *
18	5 mo.	F	18.7 *
19	2 yr.	M	18.8
20	10 yr.	F	19.1
21	21 mo.	M	19.4
22	5 yr.	M	19.6 *
23	16 yr.	F	19.6 *
24	2½ yr.	M	19.6
25	6 yr.	F	20.2
26	2 yr.	M	20.7
27	14 yr.	M	20.7 *
28	7 yr.	F	20.8 *
29	3 mo.	F	21.1 *
30	2 yr.	F	21.7
31	10 yr.	F	21.7 *
32	2 mo.	M	21.9 *
33	7 yr.	M	22.3
34	3 wk.	M	22.4
35	6 yr.	F	22.5
36	12 yr.	M	22.6
37	10 yr.	F	23.3
38	7½ yr.	M	23.5
39	6 yr.	F	23.5
40	8 yr.	M	23.6
41	4½ yr.	M	23.8
42	11 yr.	F	23.8
43	9 yr.	M	24.0
44	10 yr.	M	24.1
45	2 yr.	F	24.2
46	20 mo.	F	24.4
47	2 yr.	M	24.4 *
48	4 yr.	M	24.6
49	8 yr.	M	24.6
50	5 yr.	M	24.9
51	11 yr.	M	24.9 *
52	13½ yr.	M	25.0
53	1 yr.	F	25.0
54	12 yr.	F	25.4
55	4 yr.	M	25.7
56	3½ yr.	M	26.0
57	2 yr.	M	26.4
58	9 yr.	M	27.0
59	7 yr.	F	27.7
60	15 yr.	F	27.8
61	7 yr.	M	28.9
62	12 yr.	M	30.8
Av. or mean			21.4
S. D.			±4.12

* Subjects in whom more than one blood determination was performed on different days (see Table 2).

TABLE 2.—*Serial Fasting Blood Plasma Pepsinogen Determinations in Same Subjects*

Case	Age	Sex	Serial Blood Plasma Pepsinogen Values Expressed as Pepsinogen Units (P.U.%) 1	2	3	4	5	6	Average of All	Standard Deviation	Percentage Difference Between Specimens
5	8 mo.	F	15.6(1/29) *	15.2(2/6)					15.4	±0.2	2.5
8	1 yr.	F	17.6(3/11)	15.8(3/13)					16.7	±0.9	10.0
9	10 yr.	M	15.7(2/6)	17.7(2/9)					16.7	±1.0	11
16	11 yr.	F	18.2(3/13)	19.6(3.18)	18.2(3/20)				18.6	±0.6	0.6
17	5 mo.	F	20.2(5/3)	17.3(5/7)					18.7	±1.5	14
21	5 yr.	M	15.8(1/11)	23.4(1/15)					19.6	±3.8	22
22	16 yr.	F	18.1(2/6)	20.3(2/9)	18.1(3/5)	24.2(3/11)	25.4(3/18)	17.6(3/20)	19.6	±2.68	23
26	14 yr.	M	19.7(1/24)	20.3(1/26)	22.1(1/28)				20.7	±0.98	11
27	7 yr.	F	20.2(6/10)	21.4(6/11)					20.8	±0.6	5
28	3 mo.	F	24.9(1/8)	17.3(1/23)					21.1	±3.8	30
30	10 yr.	F	24.2(1/9)	20 (2/6)	18.8(2/11)	23.8(2/13)			21.7	±2.3	10
31	2 mo.	M	25.0(1/6)	18.8(2/13)					21.9	±3.1	24
46	2 yr.	M	27.3(2/28)	21.5(2/29)					24.4	±2.9	21
51	11 yr.	M	23 (2/6)	26.8(2/9)					24.9	±1.9	14
										±2.66	14.2

TABLE 3.—*Twenty-Four-Hour Urine Pepsinogen (Uropepsin) Excretion in Normal Children*

Case	Sex	Age, Yr.	24-Hour Uropepsin Excretion, Units	Uropepsin Excretion, Units/Hr.	Uropepsin Excretion in 3 Different 24 Hr. Urines 1	2	3	Maximal Percentage Difference
1	F	12½	900	37.5				
2	M	12	990	41.2				
3	M	1½	1,080	45.0				
4	M	14	1,233	51.2	1,268	1,182	1,240	6.8
5	F	8	1,270	52.9				
6	F	12	1,315	54.7				
7	M	7	1,320	55.0				
8	F	11	1,330	55.4				
9	M	6	1,335	55.6				
10	M	3 mo.	1,388	57.8	1,520	1,412	1,232	12.3
11	M	10	1,410	58.7				
12	M	6	1,416	59.0				
13	F	11	1,420	59.1	1,516	1,360	1,384	11.1
14	M	11	1,524	63.5				
15	M	11	1,570	65.4				
16	F	10	1,575	65.6				
17	M	9	1,656	69.0	1,524	1,788		11.7
18	M	3	1,686	70.2				
19	M	11	1,730	72.0				
20	F	12	1,742	72.5	1,722	1,545	1,960	12.7
21	M	8	1,796	74.8				
22	F	12	1,870	77.9				
23	F	10	1,930	80.4				
24	F	12	1,983	80.5	2,005	1,780	1,945	11.9
25	M	16	1,970	82.0				
26	F	15	2,000	83.0				
27	M	13	2,045	85.2	2,006	2,183	1,856	11.7
28	M	12	2,066	86.1				
29	M	4	2,130	88.7				
30	M	13	2,140	89.1				
31	F	9	2,268	94.5				
32	M	13	2,340	97.5	2,330	2,420	2,270	10.6
33	M	12	2,360	98.3				
34	M	9½	2,400	100.0				
35	M	12	2,560	106.6				
36	M	12	2,880	120.0				
Av.			1,738	72.4	1,789	1,706	1,699	11.1
S. D.			±456	±19.2	±336	±304	±378	

2880 uropepsin units, with a mean of 1738 units and a standard deviation of ±456 units. Expressed as uropepsin units excreted per hour, the values varied from 37.5 units to 120 units per hour, with a mean of 72.4 units per hour and a standard deviation of ±19.2 units per hour (Table 3).

Eight children, in each of whom 3 different 24-hour urine collections were made on different days, showed a range of maximum percentage difference that varied from 6.8% to 12.7% (Table 3).

B. Twelve-hour overnight urine collections in 33 normal children showed a range from 245 to 1450 uropepsin units excreted in 12 hours, with a mean of 749 units and a standard deviation of ±352 units. If we multiply these results by two in order to obtain the theoretical 24-hour urine collection, we have a range of 490 to 2900 uropepsin units excreted in 24 hours and a mean of 1498 uropepsin units and a standard deviation of ±704 units. Calculating the results on a per hour excretion basis, we have a range of 20.4 to 120.8 uropepsin units in the 12-hour urine collection (Table 4).

C. Single three- to four-hour urine collections in one group of 25 normal children gave a uropepsin hourly excretion rate that ranged from 24.2 to 159.0 uropepsin units with a mean of 63.3 uropepsin units and a standard deviation of ±33.8 uropepsin units (Table 4). In the second group, of 21 nor-

TABLE 4.—*Comparison of Various Measurements of Uropepsin Excretion*

		Multiple Single 3-4 Hr. Urine Specimens, Uropepsin Units/Hr.				12 Hr. Night Urine Collection (8 P. M.-8 A. M.) Uropepsin Units			
Case	Single 3-4 Hr. Urine Collection, Uropepsin Units/Hr.	Av. Excretion of 1+2+3	Single 3-4 Hr. Specimens 1	2	3	Total 12 Hr. Uropepsin Excretion	Theoretical 24 Hr. Uropepsin Excretion	Uropepsin Units/Hr.	Urine Excreted in 12 Hr., Ml.
1	24.2	32.0	44.3	20.0		245	490	20.4	704
2	28.2	33.0	38.0	28.0		278	556	23.16	780
3	33.0	34.1	42.7	25.7		290	580	24.16	928
4	35.8	35.5	25.4	45.6		340	680	28.3	352
5	36.2	38.7	36.4	33.3	36.5	340	680	28.3	768
6	37.2	40.4	37.8	43.0		380	760	31.6	,050
7	38.0	41.2	73.3	22.6	27.9	417	834	34.75	512
8	38.0	43.6	30.2	32.7	68.0	417	834	34.75	448
9	40.2	49.5	53.8	45.2		443	886	36.9	410
10	42.7	50.2	39.6	147.0	70.5	456	912	38.0	512
11	43.3	51.4	82.6	71.7		488	976	40.6	320
12	44.8	59.3	98.2	49.7		562	1,124	46.8	540
13	48.0	61.2	40.2	82.2		595	1,190	49.5	480
14	53.8	71.4	56.5	86.3		617	1,234	51.4	450
15	56.8	71.4	75.9	97.7	40.6	620	1,240	51.6	448
16	62.5	80.8	56.6	82.8	103.0	623	1,246	51.9	672
17	71.0	84.5	88.5	80.6		675	1,350	56.2	448
18	73.2	85.2	32.4	138.0		695	1,390	57.9	1,410
19	84.6	105.4	138.0	90.5	78.8	697	1,394	58.0	896
20	92.8	115.0	98.2	149.0	108.0	834	1,668	69.5	288
21	98.2	123.5	134.0	113.0		900	1,800	75.0	515
22	101.0					903	1,806	75.2	704
23	114.0					934	1,868	77.8	480
24	123.0					995	1,990	82.9	600
25	159.0					1,020	2,040	85.0	576
26						1,080	2,160	90.0	672
27						1,090	2,180	90.8	640
28						1,130	2,260	94.16	1,140
29						1,240	2,480	103.3	360
30						1,240	2,480	103.3	1,740
31						1,340	2,680	111.6	390
32						1,400	2,800	116.6	416
33						1,450	2,900	120.8	420
Mean	63.3	62.3	61.8	71.1	69.2	749	1,498	62.46	
S. D.	±33.8	±31.9	±31.9	±40.5	±26.0	±352	±685	±22.2	

TABLE 5.—*Statistical Analysis of Uropepsin Values* *

Group	Uropepsin Excretion, Units/Hr. >61.0	<61.0	Total
I. 24 hr. excretion	23	13	36
II. 12 hr. excretion	13	19	32
Total	36	32	68

χ^2=3.7; P=<0.10,>0.05

	Uropepsin Excretion, Units/Hr. >59.1	<59.1	Total
I. 24 hr. excretion	23	13	36
III. Single 3-4 hr. excretion	10	15	25
Total	33	28	61

χ^2=3.4; P=<0.10, >0.05

* Method of statistical analysis is from Fisher,[9] p. 89. P is for one degree of freedom.

mal children, where two to three different three- to four-hour urine collections were made, the range was from 20.0 to 149 uropepsin units, with a mean of 62.3 uropepsin units and a standard deviation of ±27.1 uropepsin units (Table 4).

A statistical analysis of uropepsin values for comparison of data obtained with a 24-hour urine collection and with a 12-hour overnight urine collection and of data from a 24-hour urine collection and from single 3- to 4-hour urine specimens is given in Tables 6 and 7. In spite of there being much less variation in the range and standard deviation of the 24-hour urine collection than in the 12-hour and single 3- to 4-hour urine specimens, no statistically significant difference between any of the collections was found (Table 5).

Comment

Pepsinogen is secreted in the form of an inactive precursor which is activated at first by the hydrochloric acid of the gastric juice to yield pepsin itself. This pepsin then activates more pepsinogen so that the succeeding activation of pepsinogen is an "autocatalytic process."[10,11] Pepsinogen has been obtained in crystalline form.[12] The optimum pH for activation of any other gastric proteolytic enzyme is considerably less acid than that for pepsin,[13] which is about 2.0. This makes it possible to devise a method where the pH is so low that no other proteolytic enzyme but pepsinogen can become activated, and its quantitative determination can thus be accurately executed.

It is presumed that the source of the proenzyme, pepsinogen circulating in the blood and excreted in the urine,[1] is the secretion of the peptic cells of the stomach, because it is absent from the urine of the totally gastrectomized animals[14-16] and also absent in patients with achylia gastrica of pernicious anemia[17-20] or in the dogs in which surgical destruction of the gastric mucosa has been performed.[21] There is other physiologic, pharmacologic, chemical, and histologic evidence[13,22-32] that suggests that the peptic cells of the stomach produce all or the greater portion of pepsinogen. There is a possibility that pepsinogen may be produced in small amounts in the esophagus[13] and that enzymes resembling pepsin are present in mammalian cells, but very little is known of their physiologic role.[10]

The physical and chemical properties of this proenzyme obtained from gastric mucosa are similar to those of the pepsinogen obtained from the blood and urine.[6,10,11,13] Intravenous administration of pepsinogen but not that of pepsin will result in a proportionate increase in uropepsin excretion in the urine.[6,7]

Most of the pepsinogen elaborated by the peptic cells (or chief cells) is secreted into the lumen of the stomach and in the acid medium becomes the active enzyme pepsin. This is the exocrine secretion. However, a small portion of this proenzyme, pepsinogen, goes directly into the blood stream and is subsequently excreted by the kidneys, apparently unaltered. This fraction of pepsinogen production by the peptic cells is called the endocrine secretion.[22-25]

In the present discussion we shall confine ourselves entirely to the "endocrine pepsinogen." However, we wish to call attention to the fact that agents that affect

the exocrine secretion of pepsinogen do not necessarily affect the endocrine portion. There need not be a qualitative or quantitative correlation between the contents and amount of gastric juice and the blood or urine pepsinogen values.[13,18,32,33,35,36] No vagal or sympathetic nerve stimulant or depressant exercises any influence upon blood or urine pepsinogen levels.[33-35,37] Dragstedt and his co-workers[35] and others[33,34] noted no effect after vagotomy. Caffeine, histamine, insulin, pilocarpine, prostigmine, acetylcholine, choline, lecithin, atropine, and smoking, agents that affect the exocrine secretion, do not exercise any influence upon blood pepsinogen levels or urinary pepsinogen excretion.[7,13,20,23,38,39]

Conclusive knowledge regarding the regulatory mechanism of endocrine production of blood pepsinogen and its excretion into the urine is lacking. However, there is a sizable array of experimental and clinical data which is circumstantial and inferential which supports the hypothesis that the hypothalamic-pituitary-adrenal axis has an influence upon pepsinogen production and may be responsible for the maintenance of the integrity and function of the peptic cells. In fact, in passing, we may add that this system operates similarly in affecting the salivary, pancreatic, and renal secretory cells.

Thomas Addison[40] in 1855 called attention to the occurrence of severe gastrointestinal disturbance in adrenocortical deficiency in man. More recent studies[27,28,41-45] demonstrated that, in addition to reduction in absorption of fat, glucose, and sodium chloride, there are other changes in Addison's disease, such as reduction in weight of the mucosa of the gastrointestinal tract, reduction in volume of gastric secretion of hydrochloric acid and pepsin, and decrease in the size of the villi. Introduction of salt improves the water and salt metabolic state and restores glucose absorptive rate, but has no effect on fat, digestive juices, or the anatomic structure of the gastrointestinal tract. Only the administration of the glucocorticoid hormone restores the condition to normal.[27,29,31,32]

Hypophysectomy and/or adrenalectomy[27-32] induce similar significant cytological and chemical changes. Excision of all other endocrine glands results in no such alteration.[29,32] It appears that the pituitary glands exert their control through the adrenal cortex. This is supported by the fact that corticotropin (ACTH) or glucocorticoids restore the anatomical and physiological condition by replacement therapy only if the adrenal glands are intact.

Patients with panhypopituitarism and with adrenal insufficiency or subjects after adrenalectomy (man and animals)[4,47,48] showed a marked reduction in pepsinogen production and excretion. With replacement glucocorticoid therapy, these patients and animals demonstrated a sharp rise to normal or above-normal levels, depending upon dosage.

On the other hand, in patients with hyperpituitarism or hyperadrenocortism there is an increased pepsinogen secretion and excretion.[4,47,48]

These facts further emphasize the correlation between the function of the peptic cells and the pituitary and adrenal glands.

Corticotropic or glucocorticoid hormone administered in large doses over an adequate period produced significant increases in pepsinogen output in man.[3,4,47-59] Short-term administration of the above hormones has been found to increase pepsinogen secretion in only a limited number of subjects.[47,48,58] A similar effect has been demonstrated in vagotomized or denervated stomach or antrectomized animal and man.[13,17,47,48] Furthermore, an increase in plasma pepsinogen ocurred in the gastric-venous blood after adminstration of corticotropin which was even greater than that in blood obtained from other blood vessels. This increase, even if very high in the gastric venous blood, may not be reflected in the peripheral blood, because of dilution.[26,48,60,61]

The corticotropic factor of the anterior pituitary and the glucocorticoids, such as cortisone, hydrocortisone (compound F), corticosterone (compound B), and prednisone, are the only hormones that affect

peptic activity.[13,47] No response was noted after prolonged administration of growth, thyrotropic, or gonadotropic hormones of the anterior pituitary[13,47]; dexoycorticosterone[62]; testicular and adrenal androgens; progesterone, and estrogens.[13,29,32,47,63] An exception may be made of the thyroid hormone, which has been found to have an indirect or secondary influence on peptic activity by its direct or primary effect on the adrenal cortex. There is anatomical and physiological evidence of such an effect.[4,29,32,47,64]

Statistical correlated studies of uropepsin and adrenal steroid excretion have been performed by Gray et al. and others.[4,40,48] They found increased excretion of uropepsin and 17-hydroxycorticoids in the urine in Cushing's disease and in normal subjects receiving corticotropin and the converse in Addison's disease and in hypopituitarism.

All the foregoing data lend support to the theory of a relationship between pituitary-adrenal cortical activity and pepsinogen formation. However, whether the functional state of pepsinogen production as reflected by blood plasma pepsinogen levels or uropepsin excretion reflects the state of adrenal glucocorticoid activity is highly controversial. This concept has not been definitely established and accepted by all and requires further study. The sensitiveness of peptic function to adrenal function and its magnitude of response are still matters to be determined in investigations where correlation between pepsinogen and glucocorticoids in blood and urine must be closely defined and established.

Our results confirm those of Mirsky et al.[1] and Hirschowitz[2,13] and others[36] that the blood plasma pepsinogen levels remain at relatively constant levels throughout the day and are independent of activity and food intake and composition. The same is partially true of uropepsin excretion,[3,4,6,18,66] although certain investigators have noted significant variations during the 24-hour period, especially differences between day and night urines.[33,52] In the present study a statistical analysis revealed no significant differences between single 3- to 4-hour urine specimens, 12-hour overnight urines, and the total 24-hour urine collections. This was noted in spite of the fact that there was a narrower range of variation and a smaller standard deviation in the 24-hour urine collection group.

Normal blood and urine pepsinogen values in infants and children were obtained. The blood values ranged from 10.5 to 30.8 P. U. %, with a mean of 21.4 P. U. % and a standard deviation of ±4.12 P. U. %. Hirschowitz's[2] values were from 6.9 to 20.8 P. U. %. The 24-hour urine values ranged from 900 to 2880 units, with a mean of 1738 units and a standard deviation of ±456 units. Spiro et al.[3] found normal values from 1050 to 3100 units in 24 hours.

Variations of blood plasma pepsinogen or the 24-hour uropepsin excretion in the same person were not great and were much less than those found in the entire group of normal persons. The range of normal values does not render these results less meaningful, since we are interested in statistically valid values that are significantly above or below the normal range, and in the same person we are similarly concerned with definite changes in pepsinogen values under different conditions. The reasons for the wide normal range of pepsinogen values are unknown, but there are a few tempting speculations, which need not be mentioned here but which should be fortified with further experimental data.

Summary

Blood plasma pepsinogen values in 62 normal infants and children ranged from 10.5 P. U. % to 30.8 P. U. %, with a mean of 21.4 P. U. % and a standard deviation of ±4.12 P. U. %.

Twenty-four-hour urine uropepsin excretion in 36 normal infants and children ranged from 900 units to 2880 units, with a mean of 1738 units and a standard deviation of ±45.6 units.

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Blood Plasma Pepsinogen in Acute Infections in Infants and Children

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At present, the physiologic and clinical significance of blood plasma pepsinogen is not known and awaits further investigation. Under normal conditions, in normal persons including infants and children,[1-6] the blood plasma pepsinogen concentrations have been shown to vary within certain limits and to be independent of food, ordinary psychic influences, and practically all agents which usually stimulate or depress the gastric juice concentration of pepsinogen and pepsin. All the factors responsible for the magnitude of variability of blood plasma pepsinogen in the normal subjects are unknown. There is some circumstantial and inferential evidence that the anterior pituitary-adrenal cortical system may influence the production of the endogenous or endocrine fraction of pepsinogen by the peptic cells of the gastric mucosa[3,7-25] and therefore the levels of blood plasma pepsinogen. Since in acute infections there may be anatomical or functional disturbances of the adrenal gland or both,[26-30] it was thought that the study of blood plasma pepsinogen levels during the acute febrile and postfebrile periods of acute infections should be of interest, and this is reported herewith.

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Methods and Results

Seventy-four infants and children with a variety of acute infections were studied. With the exception of five children, all had had fever for one week or less. No subacute or chronic infections were included in this series. All were acutely ill at the time that the investigation was instituted and had a temperature of 101 F or over.

Three to five milliliters of blood was withdrawn in the morning before breakfast, and blood plasma pepsinogen determinations were made as described by Hirschowitz.[3] One or more samples were taken on different days during the acute febrile period and during the postfebrile period. The results are summarized in the Table.

The Table presents results on 74 children with miscellaneous acute infections. The results were obtained on the dates specified in the Table and related to the date of onset of the acute infection and to the first afebrile day. These values are compared in the Table with those that have been established as normal for infants and children of similar ages.[5] The blood pepsinogen values are expressed as pepsinogen units per 100 ml. of blood (P. U. %), a standard adopted by Hirschowitz.[2] In our previous study,[5] with normal infants and children, the normal P. U. % range was from 10.5 to 30.8 P. U. %, with a mean of 21.4 P. U. % and a standard deviation of ±4.12. In the present study during the febrile period the P. U. % range was from 6.6 P. U. % to 64.3 P. U. %, with a mean of 30.1 P. U. % and a standard deviation of ±10.7 P. U. %.

Closer analysis reveals that during the febrile period, of 74 subjects, only 2 had values under 10 P. U. %; 3, between 10 and 15 P. U. %; 7, between 15 and 20 P. U. %; 27, between 20 and 30 P. U. %, and 35 patients, over 30 P. U. %. Thirty-five

Blood Plasma Pepsinogen Levels in Infants and Children with Acute Infections *

Case	Age	Sex	Diagnosis	Febrile Period: Days Before 1st Blood Specimen	Febrile Period: Blood Plasma Pepsinogen (P. U. %) & Date Blood Specimens Obtained			Febrile Period: Av. P. U. %	First Afebrile Day	Afebrile Period: Blood Plasma Pepsinogen (P. U. %) & Date Blood Specimens Obtained			Afebrile Period: Av. P. U. %
1	6½ yr.	F	Pneumonia	7	6.6 (2/2)			6.6	2/4	20 (2/6)	15.1 (2/8)		12.6
2	5 mo.	F	Roseola infantum	3	8.4 (1/28)			8.4	1/29 (rash)	12.2 (1/29)	14.6 (1/31)		13.5
3	2 yr.	M	Acute infectious arthritis	7	11.5 (2/6)			11.5	2/9	15.7 (2/11)			15.7
4	7 yr.	M	Acute osteomyelitis	3	12.2 (1/16)	8.3 (1/17)		10.3	1/25	10.4 (2/1)	18.5 (2/8)	19.3 (2/13)	16.1
5	8 yr.	M	Cellulitis & abscess of left leg	3	13.8 (5/16)			13.8	5/18; operation 5/19	22.7 (5/23)	18.5 (5/25)		20.6
6	13 yr.	M	Osteomyelitis	6-7	15 (2/2)			15	2/6	17.4 (2/10)	16.4 (2/15)		16.9
7	4 yr.	F	group, respiratory infection	2	15.6 (1/29)			15.6	2/1	15.2 (2/6)			15.2
8	11 yr.	M	Osteomyelitis	3	16.3 (4/3)			16.3	4/8	21.5 (4/8)	18.8 (4/10)		20.2
9	2 yr.	M	Probable viral infection (F. U. O.)	10	16.8 (5/19)			16.8	5/21	10.6 (5/21)	14.7 (5/23)		12.7
10	9 days	F	Purulent meningitis	1	17.3 (1/10)	23.0 (1/11)	Died 1/12	20.2		Died	1/12		
11	13½ yr.	F	Pneumonia with pleurisy	3	18.4 (1/27)			18.4	1/30	10.8 (2/1)	15.2 (2/8)		13
12	1 mo.	F	Laryngotracheitis (2/28) and otitis media (3/11)	1	19.0 (3/1)	22.6 (3/11)		20.8	3/13	25.0 (3/18)			25
13	5 yr.	F	Pyelonephritis	5	21.8 (5/9)	27.4 (5/14)	31.5 (5/16)	26.9	5/20	19.1 (5/28)			19.1

* Listed in order of magnitude of the first blood plasma pepsinogen determination.

*Blood Plasma Pepsinogen Levels in Infants and Children with Acute Infections**—Continued

Case	Age	Sex	Diagnosis	Days Before 1st Blood Specimen	Febrile Period: Blood Plasma Pepsinogen (P. U. %) & Date Blood Specimens Obtained	Av. P. U. %	First Afebrile Day	Afebrile Period: Blood Plasma Pepsinogen P. U. %) & Date Blood Specimens Obtained	Av. P. U. %
14	3½ yr.	M	Cellulitis of hand	1	22.3 (2/14)	22.3	2/16	22.5 (2/20)	22.5
15	12 yr.	M	Acute osteomyelitis	2	22.6 (2/14)	22.6	2/17	18.8 (2/23) 16.6 (2/27)	17.7
16	8 mo.	M	Abscess near right shoulder	6	23.7 (5/14)	23.7	5/16	14.7 (5/25) 18.0 (5/26) 22.1 (5/27) 23.2 (5/28)	19.5
17	4 yr.	F	Respiratory allergy & pneumonia	3	23.8 (2/13) 21.1 (2/15)	22.5	2/20	14.6 (2/26)	14.6
18	11 yr.	M	Pleural effusion	8	24.0 (1/23)	24.0	1/25	17.7 (1/29)	17.7
19	2 yr.	F	Probable viral infection (F. U. O.)	10	24.2 (1/15) 22.4 (1/18)	23.3	1/21	19.3	19.3
20	11 yr.	M	Infectious arthritis	7–8	24.2 (4/17) 18.0 (4/19)	21.1	4/23	26.4 (4/24) 26.8 (4/29) 28.0 (5/4)	27.1
21	7 yr.	F	Pneumonia	7	24.9 (5/10)	24.9	5/13	11.5 (5/13) 21.5 (5/15) 29.8 (5/27)	20.9
22	8 wk.	M	Respiratory infection	3	25.1 (1/25)	25.1	1/27	16.1 (2/11)	16.1
23	7 wk.	M	Bronchiolitis	4	27.5 (1/16)	27.5	1/18	22.6 (1/24)	22.6
24	13 yr.	M	Acute gastroenteritis	2	27.7 (6/11) 28.2 (6/12)	28	6/13	23.7	23.7
25	5 yr.	M	Left axillary adenitis	3	28.0 (1/23)	28	1/26	17.7 (1/29)	17.7
26	5 mo.	M	Bronchopneumonia	3	28.1 (1/26)	28.1	1/31	13.1 (2/1)	13.1

27	3 yr.	M	Laryngotracheitis	2	28.2 (4/18)	28.2 (4/24)		28.2	4/26	20.7 (4/29)			20.7
28	6 wk.	M	Bronchiolitis	3	28.4 (1/16)			28.4	1/18	25.2 (1/18)	19.6 (1/22)		19.6
29	8 yr.	F	Acute nasopharyngitis & tonsillitis	1	28.5 (1/16)			28.5	1/18	28.1 (1/21)			28.1
30	11 yr.	M	Bronchiectasis with recurrent fever	2 1	28.7(1/21) 30.6(3/11)			29.7	1/24 3/13	21.7(1/25) 31.5(3/13)	26.8 (3/20)	18.2 (3/27)	28.2
31	11 mo.	F	Gastroenteritis, parenteral	3	28.9 (4/15)			28.9	4/18	18.6 (4/21)			18.6
32	7 mo.	F	Pneumonia	4	29.0 (4/24)			29.0	4/27	25.1 (4/28)			25.1
33	4 yr.	F	Streptococcic throat & arthritis	4	29.0 (4/9)	21.8 (4/10)		25.4	4/11	28.9 (4/15)			28.9
34	5 yr.	M	Cervical adenitis	6	29.2 (1/15)			29.2	1/19	23.5 (1/21)			23.5
35	6 yr.	M	Mumps	1	29.2 (3/15)			29.2	3/19	13.5 (3/24)			13.5
36	12 yr.	M	Mesenteric lymphadenitis	1	29.2 (2/20)			29.2	2/25	20.9 (3/5)			20.9
37	3 mo.	F	Bronchopneumonia	5	29.4 (2/8)			29.4	2/11	24.1 (2/11)	23.3 (2/15)		23.7
38	8 mo.	F	Acute gastroenteritis, parenteral	1	29.8 (4/23)			29.8	4/25	20.8 (4/25)			20.8
39	4 yr.	M	Acute tonsillitis	5	29.8 (5/15)			29.8	5/17	19.3 (5/23)			19.3
40	5 yr.	M	Lymphocytic choriomeningitis	2	30.2 (6/10)			30.2	6/13	30.4 (6/14)	27.0 (6/18)		28.7
41	5 yr.	F	Viral infection (gastroenteritis)	3	30.2 (4/30)				5/3	12.7 (5/7)			12.7
42	9 yr.	M	Mesenteric lymphadenitis	1	30.2 (1/27) 30.6			30.2	1/27	23.2 (2/1) 23.6			23.2

* Listed in order of magnitude of the first blood plasma pepsinogen determination.

*Blood Plasma Pepsinogen Levels in Infants and Children with Acute Infections**—Continued.

Case	Age	Sex	Diagnosis	Days Before 1st Blood Specimen	Febrile Period: Blood Plasma Pepsinogen (P. U.%) & Date Blood Specimens Obtained	Av. P. U. %	First Afebrile Day	Afebrile Period: Blood Plasma Pepsinogen (P. U.%) & Date Blood Specimens Obtained	Av. P. U. %
43	13 yr.	M	Mumps	1	(3/15)	30.6	3/21	(3/26)	28.6
44	11 mo.	M	Parenteral diarrhea	3	31.4 (1/9)	31.4	1/22	18.3 (1/16)	18.3
45	6 mo.	F	Bronchopneumonia	2	31.4 (5/10)	31.4	5/11	15.4 (5/15)	15.4
46	2 yr.	M	Bilat. ethmoiditis	3	31.5 (5/12)	31.5	5/14	24.9 (5/14) 12.2 (5/16)	18.6
47	8 yr.	M	Ac. rheum. fever	2	32.3 (5/6) 20.3 (5/8)	26.3	5/13	12.8 (5/15)	12.8
48	12 days	F	Parenteral diarrhea	5	32.6 (1/23) 29.0 (1/25)	31.8	1/26	14.7 (1/28)	14.7
49	4 mo.	F	Infectious arthritis	3	32.7 (4/30)	32.7	5/1	13.2 (5/4) 25.3 (5/7) 19.1 (5/28)	19.2
50	2 mo.	F	Pneumonia	2	33.2 (2/13) 14.9 (2/15)	24.5	2/17	16.1 (2/18)	16.1
51	4 mo.	M	Bronchopneumonia	6	33.2 (4/25)	33.2	4/27	21.3 (4/30)	21.3
52	5 yr.	F	Chorea with fever & high sed. rate	5	33.2 (4/26) 25.7 (5/1)	29.5	5/3	9.4 (5/5)	9.4
53	10 yr.	M	Nasopharyng. & otitis media	3	34.6 (4/6)	34.6	4/8	18.0 (4/11)	18.0
54	3 yr.	F	Pharyng. & tonsillitis & cervical adenitis	7	35 (3/27)	35	3/30, moniliasis in throat	78.3 (4/1) 30.7 (4/5)	55.0
55	4 mo.	M	Pneumonia	5	35.2 (5/9)	35.2	5/13	26.1 (5/15)	26.1
56	5 yr.	M	Ac. rheum. fever	1	35.2 (6/17)	35.2	6/20	22.8 (6/25) 14.6 (6/30)	18.7
					35.6			13.5	

57	10 yr.	F	Streptococcic throat	1	(3/27)			35.6	4/1	(4/1)			13.5
58	9 yr.	M	Tonsillitis & cervical adenitis	3	36.4 (3/27)			36.4	3/29	23.2 (3/30)			23.2
59	11 mo.	M	Cellulitis of cavernous hemangioma	9	36.8 7(/15)	35.7 (7/17)		36.3	7/18	39.6 (7/22)			39.6
60	12 yr.	F	Bronchiectasis	7	37.2 (6/6)	32.9 (6/7)	39.5 (6/8)	36.5	6/18	34.7 (6/20)	26.9 (6/27)		30.8
61	3 yr.	F	Pyuria	3	37.4 (7/22)			37.4	7/24	12.7 (7/24)			12.7
62	6 mo.	M	Pneumonia	4	37.6 (1/9)			37.6	1/15	21.1 (1/16)			21.1
63	7 yr.	M	Acute gastroenteritis	2	39.8 (4/6)			39.8	4/10	17.9 (4/13)			17.9
64	4 wk.	M	Mastitis & cellulitis of left chest & abd.	3-5	40.2 (4/19)			40.2	4/23	22.6 (4/24)	35.6 (5/1)		29.1
65	1 mo.	M	Acute diarrhea	3	44.2 (5/14)	42.2 (5/15)		43.2	5/16	18.5 (5/23)			18.5
66	5 yr.	F	Respiratory infection	3	44.5 (5/11)	20.0 (5/13)	23.6 (5/15)	29.4	5/17	16.4 (5/21)			16.4
67	11 mo.	F	Parenteral diarrhea	2	47.0 (4/23)			47.0	4/29	20.8 (5/1)			20.8
68	10 days	F	Cellulitis & abscess of left buttock	2	48.3 (2/19)			48.3	2/25	32.3 (2/28)			32.3
69	4 yr.	F	Viral meningitis	2	49 (1/20)			49	1/30	19.7 (2/1)			19.7
70	17 mo.	M	Tuber. meningitis	5 wk. of fever	51.4 (4/23)	48.4 (5/2)		49.9	5/5	21.8 (5/9)			21.8
71	6 mo.	M	Acute osteomyelitis	4	54.6 (1/9)			54.6	1/12	21.1 (1/16)			21.1
72	17 mo.	F	Roseola infantum	2	55.2 (4/2)			55.2	4/3 Rash	39.1			39.1
73	15 mo.	M	Respiratory infection	3	16.8(3/4) Convulsion for 7 hr.		59.8 (3/5)	38.3	3/6	34.3 (3/7)			34.3

* Listed in order of magnitude of the first blood plasma pepsinogen determination.

Blood Plasma Pepsinogen Levels in Infants and Children with Acute Infections *—Continued.

Case	Age	Sex	Diagnosis	Febrile Period				Afebrile Period			
				Days Before 1st Blood Specimen	Blood Plasma Pepsinogen (P. U. %) & Date Blood Specimens Obtained		Av. P. U. %	First Afebrile Day	Blood Plasma Pepsinogen (P. U. %) & Date Blood Specimens Obtained		Av. P. U. %
74	2 mo.	F	Pneumonia	7	64.3 (4/3)		64.3	4/4	56 (4/4)	31.2 (4/7)	43.6
75	3 mo.	F	Typhoid vaccine injection (Hurler's syndrome)		29.0 (5/15) Temp. 102 F	26.2 (5/16) Temp. 100.6 F	29.1	5/19	21.2 (5/22)	8.4 (5/4) Preinjection period	14.8
						30.0 (5/18) (96 hr.) Temp. 100 F					
						Mean	30.1				20.9
						S. D.	± 10.7				± 7.9

* Listed in order of magnitude of the first blood plasma pepsinogen determination.

infants and children, or 47% had significantly elevated values.

In contrast, during the afebrile period, the range of blood plasma pepsinogen values was from 10.4 P. U. % to 78.3 P. U. %; the mean was 20.9 P. U. %, and the standard deviation was ±7.9. The highest figure, 78.3 P. U. %, was in a child who developed an extensive moniliasis in the mouth and throat during this afebrile period and whose value dropped to 30.7 P. U. % in four days. Of 74 patients, there were only 9 children, or 12% of the total, who had blood plasma pepsinogen values above 30 P. U. % during the postfebrile stage.

The Table indicates that the febrile period as compared with the afebrile period shows a definite increase in blood plasma pepsinogen-like substances ($P<10^{-2}$). When the values of the afebrile period were compared with those of a normal group,[4-6] no difference between the two groups could be established ($P>6\times10^{-1}$), showing clearly that there is a definite and significant change between the febrile and afebrile periods.[31]

We also studied one child (Case 75 in the Table) without evidence of infection during artificially induced fever. The initial blood plasma pepsinogen was 8.4 P. U. %. Triple typhoid vaccine (0.50 cc.) was administered subcutaneously, with a rise of temperature to 102 F and a blood plasma pepsinogen value of 29.0 P. U. %. Ninety-six hours later, when the temperature was only 100 F, the blood plasma pepsinogen was 30.0 P. U. %, and seven days after the injection it was 21.2 P. U. %.

Comment

It is evident that during acute infections there is a trend toward elevation of blood plasma pepsinogen levels. Two patients showed very low values; seven had low-normal levels; thirteen, normal values; seventeen, high-normal levels, and thirty-five showed elevated values, i. e., above 30 P. U. %. During the postfebrile period, all, with the exception of nine children, had normal blood plasma pepsinogen concentrations.

Since no direct measurements of steroid blood levels were made, no definite explanation for these observations can at present be made. However, in view of the possible role of the anterior pituitary-adrenal cortical system in the regulation of pepsinogen production,[7-25] it may be interesting to speculate whether the acute infections do not play a role in affecting the adrenal cortex and its function and therefore the blood plasma pepsinogen levels. Klein et al.[26] noted elevated serum corticoids in children with infection. Spink[28] found that "'normal' or increased blood concentrations of compound F were present in patients having severe infection, with and without peripheral vascular collapse." A depression of eosinophils has been reported during acute infection, with a return to normal levels during convalescence, except in cases of possible adrenal insufficiency.[29,30] The elevation of blood plasma pepsinogen during the acute stage of acute infection and the return to normal levels during the postinfectious period suggest some sort of response to stress. However, whether this rise and fall in blood plasma pepsinogen parallels the fluctuation in adrenocortical function is not yet established. Further observations and simultaneous determinations of adrenocorticoid blood and urine levels with levels of pepsinogen in the blood and urine must be made. As yet, no statement regarding the use of blood plasma pepsinogen determinations as an index of adrenocortical activity can be made.

Summary

In acute infections there is a trend in most cases toward an elevated blood plasma pepsinogen level (mean, 30.1 P. U. %, in contrast to a normal mean of 21.4 P. U. %) and a drop to normal in the postfebrile period (mean, 20.9 P. U. %). This rise is statistically significant.

Fever artificially induced in one patient by the administration of typhoid vaccine was accompanied by a rise in blood plasma pepsinogen (29 P. U. %), which fell to normal value a few days after the subsidence of the fever (21.2 P. U. %).

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Abnormal Sweat Electrolytes in Patients with Allergies

A Preliminary Report

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In 1953 Darling and his co-workers reported the elevation of sweat electrolytes in patients with cystic fibrosis of the pancreas. In a recent review on the physiology of sweat glands, Gochberg and Cooke [2] have listed the factors that can produce an increase in the concentration of sodium or chloride in sweat. These include hypoadrenalism, elevations of skin and rectal temperatures, increases in the rate of sweating, and prolonged diaphoresis. However, in none of these states are the changes as marked as those seen in cystic fibrosis of the pancreas.

The purpose of the present paper is to give some preliminary findings on increases in sweat electrolytes among patients with various types of allergies.

Materials and Methods

All of the allergic patients were registered in the allergy clinic of either the Children's Memorial Hospital or Northwestern University School of Medicine. The normal controls were obtained at random as part of a population survey.

Palmar sweat chlorides were estimated by the plate method described by Shwachman and Gahm.[3] In each instance the hands were washed, rinsed, and dried. Twenty minutes later, an imprint of the hand or fingers was made on the agar surface, representing the sweat accumulated during that interval. The results were classified according to a standard plate, prepared at the same time. Those imprints which were less than or equal to 25 mEq. per liter of chloride were regarded as 1+; those exceeding this and less intense than 75 mEq. per liter, as 2+; those exceeding the latter, as 3+, and those approximating or exceeding 150 mEq. per liter, as 4+. Readings of 3+ and 4+ were considered positive reactions. The sweat tests were performed by the method described by Shwachman, Leubner, and Catzel.[4] Younger infants were placed inside a plastic bag. Older patients were wrapped in a blanket and heat was applied externally by a heating pad. Family histories were obtained by questionnaire.

Results of Sweat Plate Tests

The results obtained by the sweat plate method are summarized in Table 1. It was found that 68 of 123 allergic patients (56%) showed a positive reaction. In contrast, only 128 of 1001 persons in the control group (13%) were positive. The difference is highly significant (χ^2 [1 d. f.]=138; $P<0.001$).

If one divides the data into those of adults and children (under 14 years of age), the differences are still highly significant. It was found that 27 of 53 allergic adults (51%) showed a positive reaction, while only 93 of 830 controls (11%) were found to be abnormal (χ^2 [1 d. f.]=68; $P<0.001$). Similarly, among the children,

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TABLE 1.—*Results of Sweat Plate Tests in Allergic Patients and Normal Controls Divided According to Age*

	Allergic Patients			Normal Controls		
		Positive			Positive	
	No. Tested	No.	%	No. Tested	No.	%
Adults over 14 yr.	53	27	51	830	93	11
Children under 14 yr.	70	41	59	171	35	20
Total	123	68	55	1,001	128	13

41 of 70 allergic patients (59%) and 35 of 171 normal controls (20%) showed a positive sweat plate (χ^2 [1 d. f.]=33; $P<0.001$).

The sex of the patient did not appear to influence the results, as shown in Table 2.

TABLE 2.—*Results of Sweat Plate Tests in Allergic Patients and Normal Controls Divided According to Sex*

	Allergic Patients			Normal Controls		
		Positive			Positive	
	No. Tested	No.	%	No. Tested	No.	%
Males	57	33	58	426	57	13
Females	66	35	53	575	71	12
Total	123	68	55	1,001	128	13

Among males, 33 of 57 allergic patients (58%) were positive, while 57 of 426 controls (13%) were abnormal (χ^2 [1 d. f.]=75; $P<0.001$). Among females, 35 of 66 allergic patients (53%) and 71 of 575 controls (12%) showed a positive reaction (χ^2 [1 d. f.]=71; $P<0.001$).

Next, we turn to the problem of racial background. It is generally agreed that cystic fibrosis of the pancreas rarely occurs in Negro children. From this, one can assume that the number of heterozygous carriers of that gene would also be greatly reduced among the Negro population. Since this would have considerable bearing upon the present study, the data have been analyzed in terms of racial background in Table 3. Among the white population, 48 of 78 allergic patients (62%) and 111 of 777 controls (14%) showed a positive reaction (χ^2 [1 d. f.]=104; $P<0.001$). Among the Negro population, 20 of 45 allergic patients (44%) and 17 of 224 controls (7%) were abnormal by this test (χ^2 [1 d. f.]=43; $P<0.001$). In the comparison of the incidence of positive reactions

TABLE 3.—*Results of Sweat Plate Tests in Allergic Patients and Normal Controls Divided According to Race*

	Allergic Patients			Normal Controls		
		Positive			Positive	
	No. Tested	No.	%	No. Tested	No.	%
Whites	78	48	62	777	111	14
Negroes	45	20	44	224	17	7
Total	123	68	55	1,001	128	13

among the white and Negro allergy patients, the differences are probably not significant (χ^2 [1 d. f.]=3.9; P=0.05 to 0.10). On the other hand, among the control population the differences between the white and Negro persons are significant (χ^2 [1 d. f.]= 7.4; P=0.005). Thus, it would appear that the incidence of elevated sweat chlorides as measured by the plate method is significantly lower among the Negro population as a whole. The changes among the allergic patients may at least in part be independent of that influence.

The patients were classified according to the type of allergy which was most prominent, as shown in Table 4. It is apparent that the positive tests could not be correlated with any specific diagnosis (χ^2 [3 d. f.]=4; P=0.20 to 0.30). In the same way, no special group of drugs was found to be responsible for this effect. In fact, many of the patients with positive sweat plates were taking no medications at all.

Results of Sweat Tests

Regular tests for sweat sodium and sweat chloride were performed on 32 of the patients with allergy, selected at random. These were compared with patients with cystic fibrosis of the pancreas and normal controls. The results are given in Table 5. The differences between the means for allergic patients and normal controls are statistically significant (for sweat sodium, t=5.15; P<0.001; for sweat chloride, t=2.56; P=0.01 to 0.02).

In terms of actual values, it was found that 11 of 32 allergic patients had sweat sodium levels of 50 mEq. per liter or higher (upper limits of normal in our laboratory), while only 6 of the 83 normal controls exceeded that level. This difference is, again, statistically significant (χ^2 [1 d. f.]=13.5; P=0.001).

TABLE 4.—*Results of Sweat Plate Tests in Various Types of Allergy*

	Patients, No.		
	Total	Positive	Negative
Asthma	65	37	28
Hay Fever	18	11	7
Eczema	3	0	3
Miscellaneous	37	20	17
Total	123	68	55

TABLE 5.—*Results of Sweat Tests in Allergic Patients in Comparison with Normal Controls and Patients with Cystic Fibrosis of the Pancreas*

	Sweat Sodium		Sweat Chloride	
	No.	Mean±S. E., mEq/L.	No.	Mean±S. E., mEq/L
Controls	83	21.7±1.9	83	19.5±1.3
Allergic patients	32	45.4±4.2	31	28.6±3.3
Cystic fibrosis	29	103.2±3.4	29	101.0±4.3

Comment

From the above, it would appear that both sodium and chloride in the sweat are elevated in patients with various types of allergy. The changes are not as marked as those seen in cystic fibrosis of the pancreas, but they are significantly elevated when compared with normal controls.

The cause of this abnormality is completely unknown. Gochberg and Cooke [2] have suggested that the abnormality in sweat in cystic fibrosis of the pancreas may result from an alteration in the quantity of energy available for secretion. When readily available energy is limited, a rise in concentration of solute may occur. This same mechanism could also account for the elevation of sweat electrolytes in patients with allergic manifestations.

One could also suggest several genetic explanations. It is possible that patients with allergy are heterozygous carriers of the gene which in homozygous form is expressed as cystic fibrosis of the pancreas. It is generally agreed that a diagnosis of fibrocystic disease may be made when the triad of abnormal sweat electrolytes, deficiency of duodenal enzymes, and pulmonary complications are present. In some patients with asthma at least two of these three factors are present. Several pieces of evidence tend to make such a hypothesis un-

tenable: 1. The questionnaires sent out to families with allergy do not show an excess of patients with cystic fibrosis as compared with general population. Similarly, the questionnaires sent out to families with cystic fibrosis failed to demonstrate any unusual familial tendency toward allergies. 2. A survey by means of sweat plates was done in several adult pulmonary clinics among patients with chronic respiratory disease and pulmonary emphysema. This failed to reveal any increase in the incidence of positive results as compared with the population at large. 3. None of the patients with allergy covered in the present survey was found to have gastrointestinal disturbances suggestive of a deficiency of duodenal enzymes. 4. The incidence of positive reactions in white and Negro populations suggests that the changes due to allergy and cystic fibrosis may be independent of each other.

If one assumes that cystic fibrosis and allergy are not due to the same gene, the present data would have to be explained in one of two ways. One could regard the changes in sweat electrolytes as "secondary" and not "primary" gene effects.[5] If this is the case, the occurrence of sweat abnormalities in the two conditions is purely coincidental, much as is the reticulocytosis seen in sickle-cell anemia and hereditary spherocytosis. Or, one could postulate that neither cystic fibrosis nor allergy is a condition determined by a single gene. If so, the two conditions might share a common gene abnormality with regard to the determination of sweat electrolyte concentration. The multiple gene hypothesis would fit very well with allergy. For instance, it is well known that one person in a family may get hay fever and another, eczema or that both conditions will frequently appear in the same person. As a result, the exact mode of transmission of such genes has not been worked out. On the other hand, at least four studies[6-9] have shown that cystic fibrosis of the pancreas is transmitted by a single autosomal recessive gene, which would make such an explanation difficult. It is obvious that further work is required to elucidate the mechanism for these sweat electrolyte abnormalities.

From the practical standpoint, there are now four groups of persons who may show abnormalities of sweat sodium and chloride: (1) the patient with cystic fibrosis of the pancreas; (2) heterozygous carriers of the abnormal gene within his immediate family, such as among parents, siblings, and cousins; (3) presumed heterozygous carriers of the abnormal gene in the general population, which has been variously estimated to be between 2% and 8% among unselected persons, and (4) the patient with allergy, where the abnormality may be expected to occur once in every two to four patients tested.

Summary

In the course of some studies on the frequency of the gene for cystic fibrosis of the pancreas, an abnormality in sweat electrolytes has been encountered among patients with various forms of allergies.

By the plate method for determining palmar sweat chlorides, it was found that 68 of 123 allergic patients (55%) showed a positive reaction. In contrast, only 128 of 1001 persons in the control group (13%) were positive.

By the conventional sweat test, the sweat sodium was 45.4±4.2 mEq. per liter among 32 allergic patients, as compared with a value of 21.7±1.9 mEq. per liter among 83 normal controls. Similarly, the sweat chlorides were 28.6±3.3 mEq. per liter among 31 allergic patients, as compared with a value of 19.5±1.3 mEq. per liter among 83 normal controls.

This abnormality of sweat electrolytes appears to be unrelated to age, sex, race, type of allergy, or medication used by the patients.

The significance of these findings in terms of the genetics of cystic fibrosis of the pancreas is discussed.

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Placebo-Controlled Study of Reserpine in Maladjusted Retarded Children

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It was the purpose of this study to determine if a tranquilizing drug * would be effective with a group of high-grade retarded children manifesting various behaviors that are generally reflective of personal and social maladjustment.

Although early reports have been highly enthusiastic in their appraisals of the tranquilizing agents, many of the impressive results published now seem somewhat spurious in light of careful analyses that reveal poor experimental designs, contaminated ratings, and overgeneralizations not completely warranted by the data obtained. The use of control groups was deemed of utmost importance in this study, since it was believed that the drug could not be properly evaluated without a placebo control group.

Method

Subjects.—Cottage personnel and teachers at the Wayne County Training School † submitted names of children with more difficult behavioral problems between the ages of 7 and 15. Of the 135 names submitted, 30 were chosen who seemed to present the severest problems in the joint opinion of the school principal, director of the psychology department, and child care director. Their intellectual level ranged between 50 and 85, as measured by the Stanford-Binet L test. They presented no neurological signs on the basis of a medical examination.‡ These children were divided into three groups, matched on the basis of age, sex, IQ, and length of residence. Each group was then randomly assigned to one of three treatment procedures. Table 1 presents identifying information about the groups.

Medication.—Reserpine (Eskaserp) was the medication used.§ Prepared in sustained-release capsules (Spansules) of 0.5 mg. per dose, it was administered orally to the subjects in their cottages twice a day, at breakfast and before retiring, guaranteeing 24-hour coverage. Placebos, identical in appearance, were given the control subjects. Dosage was not changed during the study. Those evaluating or rating the subjects (teachers, cottage parents, and psychologists) did not know who was receiving reserpine or placebo during the study. Prior to the study, both experimental and control groups were examined individually by the resident pediatrician, who attempted to orient each child to the forthcoming routine by informing him he would receive "something to help you feel better." Nothing of a specific nature was told the child either of the medicine he was to receive or the specific effects it was supposed to have. Distribution of the drug was accomplished by the usual routine.

At the beginning of the experiment one boy receiving reserpine complained of nasal stuffiness and

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* Reserpine (Eskaserp Spansule).

† Residential treatment-training center for 800 high-grade retarded children.

‡ Before any child was included in the experiment the social service department visited the parents of potential subjects to obtain permission for their child to take part. All but one family were willing to cooperate in the study.

§ Smith, Kline & French Laboratories, Philadelphia, supplied the reserpine and placebos used in this investigation. They also provided computational services rendered by their statistical department.

TABLE 1.—*Descriptive Data for Subjects*

	Cases, No.	Race		Age		IQ		Yr. in Residence	
		W	N	Mean	S. D.	Mean	S. D.	Mean	S. D.
Group R (reserpine)									
Boys	5	3	2	12.92	1.32	73.80	6.85	2.35	1.29
Girls	5	3	2	13.17	0.80	69.20	9.24	2.58	1.66
Group R (placebo)									
Boys	6	3	3	12.75	1.98	67.50	10.84	1.86	1.11
Girls	4	3	1	13.70	0.62	70.75	5.54	3.17	2.33
Group R-P (reserpine & placebo)									
Boys	5	2	3	13.77	0.81	74.60	2.57	2.97	1.93
Girls	5	2	3	12.98	1.03	67.20	9.70	1.65	1.23
Total									
Boys	16	8	8	13.07	1.53	71.69	8.44	2.36	1.54
Girls	14	9	6	13.26	0.92	68.93	8.65	2.42	1.81

one girl indicated that she felt drowsy. Both these conditions cleared spontaneously within a week. No other side-effects were reported during the experiment.

Design.—The experiment lasted for a period of 16 weeks, during which time the procedure described in Table 2 was followed.

Techniques.—Scores were obtained for each child in the experiment on the following tests and rating scales.

Revised Stanford-Binet Test of Intelligence: If a subject had been given a Binet L test within a period of six months prior to his inclusion in the experiment, no test was given him. All other subjects, however, received a Binet L test preexperimentally from the clinical psychologists on the staff.‖ The entire group of 30 were given the Binet M test within two weeks after the close of the experiment.

Measures of Manifest Anxiety: (1) Children's Manifest Anxiety Scale. The CMAS [8] is a 42-item questionnaire with an 11-item lie scale that serves as an index of the child's proclivity for falsifying responses to anxiety items. "Manifest anxiety" is defined by this test as the number of "yes" responses given to the items (e. g., "It is hard for me to keep my mind on anything"). Using a population of sixty-three 14-year-old boys with a mean Binet IQ of 73.3, a split-half reliability of 0.72 was obtained for the CMAS by Keller [7] in his study of the relationship of auditory memory span to learning ability.

(2) Children's Anxiety Pictures. The CAP was devised by one of us [9] and consists of 40 black and white ambiguous figures of varying shapes. Children are asked to tell what they see on the cards, and anxiety is defined as the tendency to perceive these ambiguous stimuli as representing "threatening" types of objects, such as ghosts, monsters, or robbers. A total score of weighted threatening types of responses is obtained. Test-retest reliability for this technique after four to six weeks yielded a product-moment correlation of 0.85 with a separate Training School population.

Both tests of "manifest anxiety" were administered by psychologists prior to the experiment, after the two-month period, and postexperimentally.

Behavior Rating Scales: Two types of rating scales were used by cottage personnel and classroom teachers, each incorporating the same behavioral variables. The Graphic Rating Scale was administered once each week for four months and once pre- and postexperimentally, for a total of 18 times. It enabled teachers and cottage workers to rate a particular child with a numerical value ranging from positive to negative for a specified weekly period. After one week, the rank-order correlations of these ratings for both teachers and cottage personnel centered around 0.98.

The Gardner-Thompson Rating Scale was administered prior to the experiment, after the two-month period, and postexperimentally. Adapted from a method developed by Gardner and Thompson,[4] the scale allowed teachers and cottage personnel to present global impressions of a child's behavior over two two-month periods.

The following behavioral variables appeared in the above rating scales:

(1) Manageability

(2) Motor activity (Is he fidgety, restless, or generally physically relaxed, etc.?)

(3) Talkativeness

(4) Mood (Generally happy and relaxed, or unhappy, worried, and tense?)

(5) Aggression toward other children (Does he constantly fight with others in the group, or only occasionally is he the aggressor?)

(6) Attention span (rated by teachers only)

TABLE 2.—*Experimental Design*

	1st Month	2d Month	3d Month	4th Month
Group R	Reserpine	Reserpine	Reserpine	Reserpine
Group P	Placebo	Placebo	Placebo	Placebo
Group R-P	Reserpine	Reserpine	Placebo	Placebo

‖ The psychologists, teachers, cottage personnel, nurses, and social workers cooperated in the collection of the data for this experiment.

TABLE 3.—*Comparisons of the Three Treatment Groups After Two Months*

Item	Criterion of Improvement	Mean Change			F*	P
		Group P	Group R	Group R-P		
CMAS, anxiety score	Decreased score	−0.80	0.10	2.30	0.66	Insig.
CMAS, lie scale	Decreased score	0.00	0.40	0.60	0.19	Insig.
CAP	Decreased score	−2.10	−2.20	−2.70	0.03	Insig.
Gardner-Thompson scale (school)						
Manageability	Decreased score	1.20	0.10	−0.07	2.54	Insig.
Motor activity	Decreased score	0.90	0.30	−0.60	1.31	Insig.
Talkativeness	Decreased score	1.30	0.10	−0.10	1.80	Insig.
Mood	Decreased score	1.40	−0.70	0.10	2.00	Insig.
Aggression	Decreased score	1.50	0.40	−0.40	2.13	Insig.
Attention span	Decreased score	0.30	−0.60	−0.30	0.51	Insig.
Gardner-Thompson scale (cottage)						
Manageability	Decreased score	−0.10	0.30	−0.10	0.42	Insig.
Motor activity	Decreased score	0.00	−0.30	−0.80	0.82	Insig.
Talkativeness	Decreased score	−0.40	−0.10	−0.30	0.12	Insig.
Mood	Decreased score	0.40	−0.50	−0.60	1.25	Insig.
Aggression	Decreased score	0.60	0.70	−0.60	3.45	0.05
Graphic rating scale (school)						
Manageability	Decreased score	0.50	0.40	0.90	0.28	Insig.
Motor activity	Decreased score	0.30	0.80	0.30	0.27	Insig.
Talkativeness	Decreased score	0.70	−0.10	−0.10	0.99	Insig.
Mood	Decreased score	0.80	−0.40	−0.30	1.10	Insig.
Aggression	Decreased score	0.20	0.80	−1.00	6.44	0.01
Attention span	Decreased score	0.70	−0.60	−0.20	1.39	Insig.
Graphic rating scale (cottage)						
Manageability	Decreased score	0.00	−0.50	0.40	0.79	Insig.
Motor activity	Decreased score	−0.10	0.70	−0.20	0.75	Insig.
Talkativeness	Decreased score	0.20	−0.50	−0.90	1.14	Insig.
Mood	Decreased score	0.40	0.40	−0.80	2.21	Insig.
Aggression	Decreased score	0.10	−1.00	0.00	2.56	Insig.

* Between groups $d.f.$ (degrees of freedom) = 2; within groups $d.f.$ = 27.

Results

For those items on which subjects were tested or rated three times during the study (Stanford-Binet, measures of manifest anxiety, Gardner-Thompson Rating Scale) the difference between the first and third measurement was used as the improvement score. For the items on the Graphic Rating Scale (which was utilized 18 times during the study) the criterion of improvement was computed as the 1st score minus the 18th when results over a four-month period were examined and the 1st minus the 10th when the two-month data were studied. It was determined that using the 1st, 10th, and 18th Graphic scores for these analyses was as satisfactory as using an average score based on the first, middle, or last three or four weeeks' ratings.

In Table 3 are presented the results of the study as analyzed over the two-month period, while Table 4 presents comparisons for the same items over the four-month period. Analysis of variance techniques were utilized.

Inspection of both Tables reveals that, with very few exceptions, those children receiving tranquilizing medication showed no greater improvement, as measured by various psychological tests and rating scales, than did those receiving placebos.

The exceptions that did appear involved Group R-P. Following the first two-month period, during which time the subjects in this group received reserpine, significantly less aggressive behavior was noted both in the cottage (Gardner-Thompson Scale) and in school (Graphic Scale). The clarity of this finding is clouded, however, by the fact that no such improvement was demonstrated by the subjects in Group R, also receiving reserpine during the same two months. Equally unclear is the significant improvement in mood (Gardner-Thompson Scale) noted for Group R-P in the cottage after four months (Table 4). The significance of these results is considered equivocal, and, although an exact interpretation cannot be made at this time, it is possible that factors such as rater differences, type of test, or time of ratings produced, singly or in combination, the results noted for this group.

TABLE 4.—*Comparisons of the Three Treatment Groups After Four Months*

Item	Criterion of Improvement	Mean Change			F *	P
		Group P	Group R	Group R-P		
Stanford-Binet	Increased score	0.20	−2.90	−2.80	1.17	Insig.
CMAS, anxiety score	Decreased score	2.30	−0.10	2.70	0.34	Insig.
CMAS, lie score	Decreased score	0.40	1.20	1.70	0.96	Insig.
CAP	Decreased score	−1.20	0.10	−2.80	0.96	Insig.
Gardner-Thompson scale (school)						
Manageability	Decreased score	0.90	1.00	0.20	0.27	Insig.
Motor activity	Decreased score	0.90	0.80	−0.40	0.85	Insig.
Talkativeness	Decreased score	1.60	0.20	0.10	1.54	Insig.
Mood	Decreased score	1.20	−1.00	0.30	1.51	Insig.
Aggression	Decreased score	1.70	1.10	0.10	0.99	Insig.
Attention span	Decreased score	0.70	−0.80	−0.10	0.88	Insig.
Gardner-Thompson scale (cottage)						
Manageability	Decreased score	−0.10	0.60	0.60	0.98	Insig.
Motor activity	Decreased score	0.40	0.30	−0.40	1.55	Insig.
Talkativeness	Decreased score	−0.30	0.00	0.20	0.30	Insig.
Mood	Decreased score	1.00	1.20	−1.50	6.93	0.005
Aggression	Decreased score	0.40	0.40	−0.50	1.18	Insig.
Graphic rating scale (school)						
Manageability	Decreased score	−0.10	0.20	1.10	2.54	Insig.
Motor activity	Decreased score	0.50	0.40	0.70	0.10	Insig.
Talkativeness	Decreased score	0.30	0.30	0.30	0.00	Insig.
Mood	Decreased score	0.10	−0.30	0.20	0.29	Insig.
Aggression	Decreased score	0.80	0.40	−0.40	3.11	Insig.
Attention span	Decreased score	0.00	−0.80	0.10	0.81	Insig.
Graphic rating scale (cottage)						
Manageability	Decreased score	0.10	−0.10	0.70	0.45	Insig.
Motor activity	Decreased score	−0.10	0.50	0.10	0.27	Insig.
Talkativeness	Decreased score	0.40	0.40	−0.70	1.59	Insig.
Mood	Decreased score	0.30	0.50	−0.20	0.56	Insig.
Aggression	Decreased score	0.00	−0.10	0.00	0.01	Insig.

* Between groups $d.f. = 2$ within groups $d.f. = 27$.

What percentage of subjects in each group did show improvement? Improvement scores on behavioral ratings after the two-month period were utilized in this analysis, since they allowed for a direct comparison of 10 placebo and 20 reserpine subjects. Section A of Table 4 presents the behavioral ratings (Gardner-Thompson Scale) of teachers and cottage personnel expressed in terms of percentages of each group showing improvement after the two-month period, and Section B presents the differences in these percentages for the placebo- versus the drug-treated subjects. Section B reveals that with the exception of one variable (manageability, cottage) there was a greater percentage of placebo subjects showing improvement in the cottage and classroom situation than was the case for both drug groups. Although only one of these comparisons approached statistical significance as determined by a t-test, the trend seems clearly to favor the placebo subjects.

Comment

The children who received reserpine in this study did *not*, on the whole, manifest significant increases in intellectual functioning, decreases in anxiety, or improvement

TABLE 5.—*Percentage of Subjects in Three Treatment Groups Showing Improvement After Two Months (Gardner-Thompson Scale)*

Item	A. % Showing Improvement						B. Differences in % Showing Improvement, Group P vs. Groups R & R-P	
	Group P		Group R		Group R-P			
	School	Cottage	School	Cottage	School	Cottage	School	Cottage
Manageability	60	20	20	40	20	10	−40	5
Motor activity	60	30	30	20	50	20	−35	−10
Talkativeness	60	30	20	30	20	10	−40	−10
Mood	70	40	20	20	20	20	−45 *	−30
Aggression	60	50	40	60	20	10	−30	−15
Attention span	60	--	10	--	30	--	−40	--

* Significant at 5% level.

in their cottage and school behavior, in comparison with a comparable group of children receiving placebos.

One possible explanation of this finding is that a "placebo effect" produced the desired changes in certain of our control subjects. That is, the improvement that was noted for the controls might have been a function of the child's faith that the pill would do him some good, thus causing him to take steps (perhaps unverbalized to himself) to correlate his behavior with what he expected in the way of improvement. The power of the placebo effect in medicine is well documented.[12] A similar phenomenon possibly operated with our control group to effect changes equal to or greater than those produced by the actual drug. Why a similar reaction did not occur with the reserpine-treated subjects cannot be clearly ascertained at this point. More about the placebo effect needs to be learned, such as the characteristics of children most responsive and resistant to it. It is interesting to conjecture that any medicine given to this type of child carries with it the endorsement of an authority figure. This extra concrete attention, then, is all that is required to produce some positive change in behavior.

In answer to the comment that the dosage administered to our experimental subjects was too low, the recent study of Kirk and Bauer [8] can be cited. They used a population similar to ours and a dosage of reserpine ranging up to 1.5 mg. per day for a period of three months (our dosage being 0.5 mg. twice daily). Placebos were given to a control group for the same length of time. According to teachers' and cottage supervisors' ratings, Stanford-Binet and Rorschach results, and school progress reports, a greater amount of improvement coupled with a smaller amount of deterioration in adjustment and overt behavior patterns was evidenced by the placebo-treated group.¶

¶ Reference 8, p. 784.

The efficacy of drugs other than reserpine for these children can be determined only by additional research. It would seem imperative, however, that there be adequate controls in any such study if the tranquilizing agent is to be properly and scientifically assessed. There must be, among other factors, matched groups receiving identical inert facsimiles of the drug for identical periods of time; objective, quantifiable measures of improvement, and adequate secrecy measures to keep the identity of placebo and drug groups from all personnel who rate or test the subjects during the experimental period. Without such controlled procedures spurious findings can result that lead to unwarranted conclusions about what these agents can do.

Summary

The present study was undertaken to determine if tranquilizing medication is an effective therapeutic adjunct in the treatment of a population of high-grade retarded boys and girls manifesting various behavior that is generally reflective of personal and social maladjustment. Reserpine, prepared in sustained-release capsule (Spansule) form of 0.5 mg. per dose, was administered orally to the experimental subjects in their cottages twice a day for a period of two or four months. Placebos of identical appearance were given the control subjects. Thirty children were investigated. All were free of neurological signs.

Measures of intellectual functioning, indices of manifest anxiety, and behavioral ratings were gathered before, during, and after the experimental procedure. Those evaluating the subjects did not know who were receiving the medication or placebo.

With very few exceptions, statistical analyses of results indicated nonsignificant differences postexperimentally among the groups studied. A few persons receiving reserpine did show some real improvement, but this did not hold statistically for the group. In fact, for several variables the placebo group demonstrated equal or

greater gains in comparison to the experimental subjects. Significant improvement scores in aggression and mood evidenced by one experimental group were considered equivocal.

Implications of this study are discussed, and suggestions for further research in the area of chemotherapeutic procedures with children using control groups are presented. Further research with other drugs under similar circumstances is in progress.

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An Outbreak of Pharyngitis Due to Tetracycline-Resistant Group A, Type 12 Streptococci

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Although penicillin or erythromycin has been recommended as the antibiotic of choice for therapy of β-hemolytic streptococcal infections, the tetracycline drugs have been referred to frequently as alternatives in cases of hypersensitivity to the other antibiotics.[1] It has, however, been pointed out that with use of these drugs streptococci, despite their in vitro sensitivity to tetracyclines, are not eradicated, nor is rheumatic fever prevented, with nearly the degree of effectiveness obtained by administration of penicillin or erythromycin.[2-4] It is the purpose of this report to demonstrate that strains of Group A streptococci have appeared that are resistant in vitro to therapeutic levels of the tetracyclines. This should also indicate the need for concern in the commonplace use of these drugs, often without throat cultures, as broad-spectrum antibiotics for upper respiratory illnesses.

Family Outbreak

The initial outbreak was observed in a family of six with children ranging from 3 to 7 years of age. Three days after a coryzal illness involving all members, one child, aged 7, developed fever (temperature of 101 F), slight sore throat without dysphagia, and nonproductive cough. Examination of the throat revealed only moderately enlarged tonsils and nontender anterior cervical lymphadenopathy. Since pharyngeal cultures during the previous illness had been negative for β-hemolytic streptococci, therapy was begun with tetracycline, 750 mg. per day. The acute phase of the illness subsided in two days, but the drug was administered for five days. Throat cultures taken on the first, third, and seventh days after onset all contained numerous colonies of β-hemolytic streptococci. However, a minimal degree of hemolysis coupled with marked resistance to tetracycline, plus lack of reaction with grouping serum, later found to be very weak in precipitin production, caused a mistaken classification as a viridans type of Streptococcus. One weak after onset of this illness three other members of the family, one adult and two children, developed moderate sore throat with mild dysphagia and temperatures of 103 F. Chilly sensations, headache, and generalized aching also occurred. Examination revealed no pharyngeal exudate or unusual appearance of the throat, but the anterior cervical lymph nodes were enlarged to about 1 cm. and were moderately tender. Pharyngeal cultures all contained numerous colonies of β-hemolytic streptococci, Group A, Type 12, sensitive to penicillin and erythromycin but resistant to all tetracycline drugs. Phenoxymethyl penicillin (penicillin V), 1,000,000 units daily, was given orally to all members for a period of 10 days, with rapid subsidence of symptoms, and cultures were negative at termination of therapy. One week later, after the children had returned to school, throat cultures in the two oldest children again became strongly positive for Group A, Type 12 streptococci and fever and sore throat recurred. Oral therapy with phenoxymethyl penicillin was reinstituted for another 10 days, but the remaining family members with negative cultures were given

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TABLE 1.—*Results of School Throat Culture Survey for β-Hemolytic Streptococci*

Total Cultures	Group A Streptococci Isolated	Other Groups (B,G)	Type 12 *	Other Types †
131	40	4	38	2

* All resistant to tetracycline, oxytetracycline, and chlortetracycline, >30μg.
† Sensitive to tetracyclines, <10μg.

prophylactic penicillin, 250,000 units twice daily, for three days only. Weekly throat cultures were still negative one month after the second illness. Urinalyses at intervals also were within normal limits.

School Survey

Because of the known occurrence of another family outbreak in which tetracycline therapy failed to ameliorate symptoms, a culture survey was done in the school attended by children from both households. This was a private grade school with 250 pupils from upper-income families in various areas of the community. Blood agar plates were streaked immediately after the throats of approximately half of the group were swabbed. The results (Table 1) show that Group A streptococci were isolated from 30.5% of those cultured and that all but two of these were Type 12 strains that were found to be resistant to tetracyclines. Most of the positive cultures were obtained from the children in the lower grades, and practically all contained numerous colonies of β-hemolytic streptococci. There was no obvious illness in the survey group, but enlarged tonsils were commonly observed. Although complete information was not obtained, one case of acute glomerulonephritis had occurred prior to the survey and another occurred afterward.

Laboratory Studies

Streptococcal isolations were all done on 5% sheep blood agar plates. Grouping and typing were done by precipitin reactions.[5] Antibiotic sensitivity was determined on all strains initially by the disk method and read at 18 hours. Representative strains were studied further by the tube-dilution technique with purified antibiotics and read at 48 hours. The results, shown in Table 2, also confirmed the results of screening by the disk method. Also, resistance to tetracyclines was maintained after several alternating passages from blood agar to broth, but some decrease was obtained by incubating broth cultures for four days.

TABLE 2.—*Minimal Inhibitory Concentrations of Antibiotics for Group A Streptococci*

Strain	Tetracycline, μg.	Penicillin, Units	Erythromycin, μg.
Type 12			
a *	50.0	<0.04	<0.2
b *	50.0	<0.04	<0.2
c *	50.0	<0.04	<0.2
d *	50.0	<0.04	<0.2
e *	50.0	<0.04	<0.2
Type 3 †	0.2	<0.04	<0.2
19 †	0.4	<0.04	<0.2
12 †	0.8	<0.04	<0.2

* Isolated in New Orleans, 1958.
† Isolated in Illinois and California, 1954-1956.

Comment

The overwhelming preponderance of strains resistant to tetracyclines in this survey indicates the probability of their widespread dissemination or occurrence. Confirmatory to this has been the subsequent isolation of similar strains from children from several other schools in the locality. Such a variation in Group A streptococci should not create a serious problem, since penicillin and erythromycin were both inhibitory in concentrations well below the therapeutic level. Nevertheless, the practice of empirical treatment of upper respiratory illnesses with tetracycline drugs because of their "broad-spectrum" activity is commonplace. In addition, because of the previous uniform susceptibility of Group A streptococci to all of the widely used antibacterial agents except the sulfonamides, it has not been the practice to determine antibiotic sensitivity of β-hemolytic streptococci. It now appears that such information is necessary if therapy with

the sulfonamides or the tetracyclines is contemplated.

A change in Group A streptococci of this nature is not surprising in view of the relative ease with which these organisms can be made resistant to the tetracyclines in vitro.[6,7] The frequency of persistence of streptococci during therapy might also be a factor in emergence of resistant forms. Whether the strains described in this report represent a widespread alteration in Group A streptococci must be determined. It is of interest to note that decreasing sensitivity of strains from other areas has recently been described, although the degree was not as great as that found in this outbreak.[8] Even if this is not a genetic change in the organism, the clinical implications are just as significant. The common usage of the tetracyclines should continue to foster the appearance of resistant strains. Such forms are not uncommon in the zone of inhibition about a disk containing this antibiotic.

It would not be reasonable in the absence of more information to assume that there might be any relationship between Type 12, Group A streptococci and antibiotic resistance. Concern is nevertheless warranted because of the previously reported relationship between Type 12 and acute glomerulonephritis.[9,10] The importance of treatment of streptococcal infections for a period of not less than 10 days for eradication of the organisms and prevention of rheumatic fever has been emphasized.[1] Although similar procedures will lower the incidence of acute glomerulonephritis, prophylaxis to limit the spread of nephritogenic organisms and recognition of the public health aspects of this disease is certainly preferable.[11,12] Selection of the proper antibiotic is obviously a requirement in these endeavors.

Antibiotics for sensitivity determinations were supplied by Dr. J. C. Sylvester, Research Division, Abbott Laboratories. Streptococcal typing was done by Paul Frank, Naval Medical Research Unit No. 4, Great Lakes, Ill., and Dr. William Pierce, Department of Microbiology, Tulane University School of Medicine.

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Water Intoxication Following Tap-Water Enemas

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Tap-water enemas have recently been incriminated as dangerous procedures, capable of producing a clinical state of water intoxication and sometimes death. Because of several fatalities reported following tap-water enemas, many pediatricians now feel that these are contraindicated in any situation and give detailed instructions to parents regarding the preparation of isotonic solutions. Hill,[1] in an editorial, reports that "the routine has been adopted in our institution of employing only isotonic saline solution for all enemas."

It is our belief that satisfactory evidence has not been presented to show that the routine use of tap-water enemas in normal persons has a deleterious effect. It is our contention that water intoxication, resulting from enemas, develops only in a child with a functionally dilated or atonic large bowel. This study will endeavor to demonstrate that the routine administration of a tap-water enema to a patient having no history of chronic constipation and with no impairment of consciousness and who is receiving no fluids intravenously carries virtually no risk.

Rowntree[2] in 1923 called attention to the clinical picture of water intoxication in man and produced a similar condition experimentally in dogs, administering fluid by either the oral or the rectal route. In 1935 Helwig[3] described the first case of fatal water intoxication induced by enema—in that instance administered by proctoclysis—and duplicated the clinical picture experimentally in rabbits. He suggested that a disturbance existed in the "normal isotonicity of the blood." In 1951 Hiatt[4] stated that 60% of 42 patients with severe megacolon gave a history of systemic reaction following tap-water enemas, 3 patients in his group having had "shocklike states." Since then, several other cases of water intoxication following tap-water enemas in patients with congenital megacolon have been reported.[5-8] Water intoxication has been described in "normal children,"[1,9] but a review of each case revealed a history of chronic constipation, and the patients were labeled "normal" because barium enema failed to show the classic findings of congenital megacolon.

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Report of Cases

CASE 1.—A 7-year-old Negro boy was admitted to Boston City Hospital in 1954 because of vomiting of three days' duration and severe diarrhea of one day's duration. He was brought to the emergency floor, where his pulse was noted to be "rapid and thready." On physical examination the abdomen was distended, bowel sounds were decreased, and questionable tenderness was present. Rectal examination revealed a tight anal stricture, behind which was palpated a large firm fecal mass.

The patient had undergone surgery at the age of 2 days, 2 weeks, 4 months, and 10 months for correction of an imperforate anus. He had always had difficulty with bowel movements, being chronically constipated and requiring frequent enemas. (At the time of admission no history was obtained regarding the possibility of enemas administered at home just before admission.)

Admission chemistry studies revealed nonprotein nitrogen of 43 mg/100 ml., serum chloride of 112 mEq. per liter, and CO_2-combining power of 33 vol/100 ml. A flat film of the abdomen on admission showed only a large bowel "loaded with fecal material." The patient continued to pass paradoxical watery movements, and administration of intravenous fluids was started.

During the first hospital days the patient received 1500 ml. of 5% dextrose and water intravenously and 910 ml. of water by mouth. It was

noted that he voided large amounts of dilute urine and appeared somewhat lethargic and weak. His pulse was 114 per minute and "thready." On the second hospital day the patient appeared restless and complained of abdominal pain. He voided large amounts of urine in bed. It was felt that the fecal impaction might have been causing intestinal obstruction, and a soapsuds and tap-water enema, amounting to approximately 2000 ml., was administered, with little return. During that day he received 1500 ml. of 5% dextrose and water and 600 ml. of isotonic saline intravenously. He was noted to become progressively more lethargic, the skin being "cold and clammy with profuse perspiration." The patient vomited "colorless material" and continued to pass large amounts of dilute urine in bed. Breathing became labored and irregular, and the patient died 32 hours after admission.

Autopsy failed to reveal any anatomic lesions other than an anal stricture. A large amount of watery fluid was noted in the large bowel. Unfortunately, postmortem electrolyte values were not obtained.

CASE 2.—A 4-year-old Negro girl was admitted to the Boston City Hospital in 1957 because of a generalized seizure beginning 15 minutes before she was brought to the emergency floor. The patient had a history of constipation since birth, Hirschsprung's disease having been ruled out by rectal biopsy. Because of severe constipation on the day of admission, the patient's mother had given her four 1 qt. tap-water enemas, with little return. After the fourth enema the patient became irritable and began to vomit. Thereafter, she became lethargic and drowsy and was noted to pass large quantities of urine in bed. The evening of admission the patient was noted to be having a generalized seizure with tonic and clonic components.

Past history is significant insofar as the patient was born prematurely and was both mentally and physically retarded, being classified as a spastic diplegic. Previous barium-enema studies had reported "a markedly dilated and atonic colon with an elongated and redundant sigmoid."

Physical examination revealed a small pale comatose Negro girl, with intermittent muscular twitchings. Temperature was 95.6 F; pulse rate, 130 per minute; respiratory rate, 32 per minute, and blood pressure, 110/80. The skin was cold and clammy. The patient was noted to void frequently. On admission serum sodium was 120 mEq. per liter; chloride, 91 mEq. per liter; potassium, 4 mEq. per liter; nonprotein nitrogen, 27 mg/100 ml., and sugar 118 mg/100 ml. Specific gravity of the urine was 1.001. Lumbar puncture was within normal limits.

Water intoxication was diagnosed, and the patient treated with intravenous hypertonic saline. She remained comatose for 12 hours but gradually became more alert and returned to her usual state of behavior on the second hospital day. The patient's mother was instructed to avoid the use of tap-water enemas in the future.

CASE 3.—A 2½-year-old white girl was admitted to the Newton-Wellesley Hospital in 1957 because of generalized seizures of several hours' duration. Eight hours before admission the patient had had a generalized seizure and was noted to be "hot." One year previously, when she had a febrile convulsion, the patient's mother had been instructed to use a cool tap-water enema to lower the patient's temperature. Therefore, she was given a 1500 ml. tap-water enema, most of which was expelled.

Two hours later the patient again began to convulse and was given another 1500 ml. enema. A physician was called, who diagnosed tonsillitis and administered penicillin intramuscularly.

Two hours before admission the patient had another generalized seizure and four or five 1000 ml. tap-water enemas were administered. Her abdomen became distended, and she vomited brownish material. The patient was brought to the accident ward, where convulsions were controlled with barbiturates given intravenously.

Physical examination revealed a drowsy febrile girl with positive findings limited to the throat, which were characteristic of follicular tonsillitis. The patient was noted to be voiding frequently. Admission chemistry studies revealed nonprotein nitrogen to be 15 mg/100 ml.; sodium, 106 mEq. per liter*; potassium, 3.9 mEq. per liter; chloride, 94 mEq. per liter, and blood sugar, 205 mg/100 ml. Specific gravity of the urine was 1.001. Lumbar puncture was within normal limits. Chemistry studies three hours after admission revealed sodium to be 118 mEq. per liter and chloride, 85 mEq. per liter. The serum water† was 4.44 ml. per milliosmole. The patient voided large amounts of dilute urine.

Water intoxication was diagnosed, but the patient was not treated with hypertonic saline because it was felt that she was correcting her hypotonicity by voiding large quantities of dilute urine. The patient gradually improved and was discharged.

* This is probably a false low value and represents laboratory error.

† Serum water determination was performed at the Massachusetts General Hospital. Normal values range from 3.45 to 3.70 ml. per milliosmol. Values above 3.70 ml. are consistent with water intoxication, while those below 3.45 ml. indicate dehydration.

Plan of Study and Methods

To determine how normal children would react to tap-water enemas, patients, ranging in age from 3 to 12 years, were selected from the pediatric wards of the Boston City Hospital. They were recovering from illnesses not involving the central nervous system or the gastrointestinal tract. Patients having a history suggestive of previous abdominal difficulties or constipation were excluded. High colonic tap-water enemas, calculated to reduce serum sodium by approximately 10 mEq. per liter if the administered fluid were completely retained and equilibrium allowed to occur, amounted to 3.5% of body weight. The children were urged to retain the enema as long as possible. Blood specimens for sodium and chloride determinations were taken just before the enema and at 30 and 60 minutes after its administration. Sodium determinations were performed by flame photometry, and determinations of chlorides, by the Schales and Schales procedure. No oral fluid intake was permitted during the hour following administration of the enema. It should be noted that our nurses considered an enema amounting to 3.5% of body weight to be approximately twice the volume routinely administered.

The total volume of fluid administered by enema was retained for an average of 11 minutes, with expulsion at that time varying in amount from 10% to 50% of the original volume. One child voluntarily retained the total amount for 35 minutes, but in most instances constant moral support had to be given to the patient to prevent immediate evacuation. This is in marked contrast to the usual home and hospital situation, where evacuation is almost instantaneous.

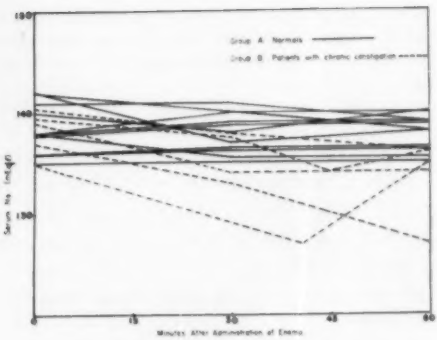
Results

In the following text and figure, Group A refers to our normal patients and Group B, to Hiatt's[4] three patients with Hirschsprung's disease and to our patients with chronic constipation to whom enemas of approximately 3.5% of body weight were administered.

As demonstrated in Figure 1, a group of 11 normal children failed to show any significant change in serum sodium after administration of tap-water enemas of 3.5% of body weight. One "normal" patient—a patient recovering from infectious mononucleosis—was not included in Group A but rather in Group B. Because this child demonstrated a marked drop in the sodium and chloride concentration of the serum at 40 minutes, the patient's mother was questioned further, and it was only then revealed that the patient had been "chronically constipated" for several years, requiring weekly enemas. Two patients with chronic constipation failed to show any remarkable elec-

Blood Sodium and Chloride Values Before and After Tap-Water Enema

Case No.	Age, Yr.	Sex	Weight, Kg.	Diagnosis	Volume of Enema Administered, Ml.	Serum Na/ Serum CL, mEq/L.		
						Before Enema	30 Min.	60 Min.
Group A								
1	7	F	25	Pediculosis	875	141/100	141/98	139/98
2	8	M	27	Pneumonia	945	142/96	137/94	138/95
3	8	M	29	Synovitis	550	142/92	139/95 (45 min.)	138/97
4	5½	F	17	Purpura	600	136/79	136/97	136/94
5	3	F	11	Pneumonia	385	136/100	137/100	137/100
6	12	F	32	Sinusitis	1100	135/93	135/95	135/93
7	6	M	21	Hematuria	735	138/98	139/99	139/98
8	7	M	25	Croup	875	138/91	136/91	136/93
9	3	M	12	Meningitis	400	140/98	138/97	140/98
10	4	F	20	Arthritis	650	138/97	140/97	140/98
11	10	F	30	Pyelonephritis	1000	136/103	130/105	139/104
Group B								
12 (Hiatt[4])	2	—	13	Cong. megacolon	400	137/—	133/130 (40 min.)	137/—
13 (Hiatt[4])	5	—	19.8	Cong. megacolon	500	140/108	138/108 134/106 (45 min.)	136/107
14 (Hiatt[4])	19	—	65	Cong. megacolon	2000	140/—	138/105	136/104
15	3	M	10	Megacolon	350	139/96	134/99	134/93
16	4½	F	19	Chronic constipation	665	136/105	127/92 (40 min.)	135/105



Serum sodium values after administration of tap-water enema, 3.5% of body weight.

trolyte change. The difference between Group A and Group B is evident.

Comment

Water intoxication may develop in several ways: through excessive oral intake, intravenous hypotonic fluid administration, proctoclysis, and hypotonic enemas. In this last category must be included barium enemas in which the barium has been suspended in tap water. Excessive amounts of hypotonic solution may be given in this manner, and in the subsequent attempts to cleanse the bowel with tap-water enemas the situation may be aggravated.[1,6,9]

Experiments with dogs have shown that the absorption of water in the large bowel is proportional to the surface area exposed to the solution.[10] Children with dilated colon, whether due to congenital megacolon or chronic constipation, are especially prone to absorb large amounts of water. The period of time during which the solution is in contact with the bowel wall is still another factor contributing to water intoxication. In our third case, the time factor probably played a more important role than increased absorptive surface. Thus, lack of ability to evacuate the bowel properly may lead to toxic symptoms in an otherwise normal person.

The symptoms of water intoxication consist of weakness, headache, lassitude, vomiting, pallor, perspiration, the production of a large amount of dilute urine, cool skin, syncope, coma, and convulsions. Wynn and Rob[11] discuss the differential diagnosis of the "hypotonic syndromes" in detail, and no attempt will be made here to review that subject.

The physiology of water intoxication is of interest. After the administration of large amounts of hypotonic solutions by rectum, ionic equilibrium takes place in the colon. Electrolytes pass from the extracellular space into the fluid "reservoir" in the bowel. Water, in turn, passes into the intravascular and extracellular space. After osmotic equilibrium has taken place, the remaining water and electrolyte in the "reservoir" are absorbed slowly into the circulation. Thus, the administered water acts first to expand the extracellular space, resulting in a drop in the concentration of serum electrolytes. For a short time the osmotic pressure of the extracellular fluid is less than that of the intracellular fluid. To reestablish tonicity, water passes into the cells. It is this effect, probably, which produces the clinical picture of water intoxication. Rowntree[2] demonstrated increased intracranial pressure in dogs receiving excessive amounts of hypotonic solutions. The central nervous system signs in our patients and those reported in the literature are in all likelihood due to an increase in intracranial pressure.

Any patient given a sufficient amount of hypotonic fluid by any route will develop water intoxication. The patients in Group A did not receive enough water to produce clinical symptoms. However, the amount administered was equivalent to two routine enemas. If these patients had been receiving dextrose and water intravenously for several days and were in a stage of incipient water intoxication, or what Rowntree calls "subacute water intoxication," a routine tap-water enema or barium enema might precipitate symptoms. In all cases of fatal water intoxication following enemas reported in the literature, hypotonic solutions were administered by several routes many times in succession before producing symptoms.

From the data obtained in our study and review of the literature, it appears that the administration of one or two tap-water enemas will not endanger the normal patient. However, tap-water enemas are contraindicated in the unconscious patient or the patient with a history of chronic constipation, where isotonic saline would be the fluid of choice. This, in itself, is not without danger, especially in the adult population, where, with compromised cardiac status, pulmonary edema may be precipitated by the administration and absorption of a large volume of saline.

Another danger inherent in the use of saline enemas would be misinterpretation on the part of the parents of the physician's instructions in the preparation of an isotonic solution. The simple substitution of tablespoonfuls for teaspoonfuls of salt can produce disastrous effects. Necrosis and slough of the distal colon following an improperly prepared saline enema, resulting in the death of a 4-year-old child, has been called to our attention.[12]

Once the condition is diagnosed, the treatment of water intoxication is simple. Administration of hypertonic saline (2% to 5%) intravenously will reestablish isotonicity and electrolyte balance. Supportive measures should be used to maintain the patient in the comatose or convulsing phase.

If the pediatrician avoids the administration of tap-water enemas to patients receiving hypotonic solutions intravenously, to unconscious or convulsing patients, and to patients with a history of severe and chronic constipation, he is extremely unlikely to encounter the problem of water intoxication.

Summary and Conclusions

Tap-water enemas were administered to 11 normal children and to 5 children with a history of severe and chronic constipation, and changes in serum electrolyte values were observed. Children with no history of central nervous system or gastrointestinal disturbances showed no significant change in serum level within one hour following the administration of tap-water enemas of 3.5% of body weight. Five children with chronic constipation, four of whom had dilated colon demonstrated by barium enema, had a decrease in the serum sodium concentration following the tap-water enema.

Three cases of water intoxication induced by tap-water enemas are presented. The physiology, symptomatology, and treatment are discussed. The factors responsible for increased uptake of water from the large bowel include increased absorptive surface area due to chronic constipation and dilatation and changes in peristaltic activity resulting in a longer period during which the hypotonic solution is in contact with the bowel wall.

If tap-water enemas are not administered to patients receiving intravenous hypotonic solutions, to unconscious patients, and to patients with chronic constipation, water intoxication is unlikely to develop. The judicious use of one tap-water enema in an otherwise normal patient is permissable and carries little risk of producing water intoxication.

Dr. Manuel Glazier gave permission to report Case 3.

818 Harrison Ave. (18) (Dr. Gellis).

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Renal Tubular and Pancreatic Islet Necrosis in Newly Born Infants

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Necrosis of the renal tubular epithelium is uncommonly encountered in newly born infants. In cases of symmetrical cortical necrosis, all elements are destroyed in areas of ischemic necrosis,[1,2] but selective tubular necrosis is limited to a few conditions. Lower nephron nephrosis or acute tubular necrosis, as we know it in adults and older children,[3] is rarely encountered during the first month of life, and in this laboratory we have seen it only once during the first week of life.

Necrobiosis of individual tubular epithelial cells may be found in infections with the virus of cytomegalic inclusion disease or herpes simplex, and the involvement is patchy. Atrophy and severe degeneration of the tubules may accompany hypoplasia with cyst formation, nephrotic syndrome,[4,5] and interstitial or chronic nephritis[6,7] in newborn infants, but frank necrosis of the tubular epithelium has not been described except in suppurative nephritides.

In a survey from this laboratory of renal circulatory diseases, Zuelzer et al.[2] described a case of lower nephron nephrosis in a 2-week-old boy. A subsequent report by Jonsson[8] related the clinical details of several cases described as lower nephron nephrosis. One infant died at 6 days of age, and although his distal convoluted and collecting tubules contained slightly pigmented casts there was no epithelial degeneration or desquamation. On the basis of the birth histories and the autopsied case, the author ascribed the urinary findings and renal changes to asphyxia neonatorum. A single case, described as lower nephron nephrosis in a newborn, has been reported by Kessel and Pepler.[9] The child was delivered after a short labor, but the amniotic fluid was meconium-stained and the infant died only 30 minutes after birth; postmortem examination showed severe aspiration of amniotic sac contents and visceral petechiae—the two interpreted as evidence of asphyxiation—and there was degeneration of the renal tubular epithelium, identical to that in the cases described below.

From among 3,556 autopsies performed on infants and children between 1940 and 1956 three cases have been selected as distinctive. One has been included among the cases of symmetrical cortical necrosis described by Zuelzer et al.,[2]* and with their permission it has been included in this report with two other, identical cases. These three infants died shortly after birth, under similar conditions, and in all three there was necrosis of the renal tubular epithelium and pancreatic islet cells.

Report of Cases

CASE 1.—A boy was admitted to this hospital at one day of age because of difficult breathing, cyanosis, and convulsions. He had been born after a normal pregnancy, but labor lasted 32 hours. Delivery was difficult and was apparently accomplished from a face presentation. His condition at birth was described as fair, and his respirations were grunting. His birth weight was 7 lb. He was placed in an incubator and given oxygen; the trachea was suctioned, but he remained cyanotic. His respirations became irregular, and his temperature rose to 105 F. He weighed 6 lb. 10 oz. and measured 20 in. in length. His temperature was 105 F, rectally. Respirations were grunting; he had a weak cry, and the skin was mottled and

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The Department of Pathology, Children's Hospital of Michigan.

* Their Case 9.

cool. A cephalohematoma was present. The heart rate was extremely rapid, and the tones were of poor quality. The respiratory rate was 40 per minute, and the lungs were clear to percussion and auscultation. The extremities were flaccid, but they seemed to move purposelessly. Instead of a Moro reflex there was a sudden, irregular flapping of all the extremities. Subdural taps were negative. Despite supportive measures, the child died eight and one-half hours after admission.

At postmortem examination, most findings were consistent with neonatal anoxia and shock. The lung was irregularly atelectatic and there were focal areas of emphysema; congestion and focal hemorrhage were also present. The brain appeared to be slightly edematous, and there were microscopic hyperemia and astrocytic swelling in the cerebral white matter. Focal petechial hemorrhages were present in the brain stem, and scattered recent areas of thrombosis were present in the cerebral choroid plexus. Slight centrolobular liver-cell necrosis and focal bland necrosis of the fetal adrenal cortex were present.

The kidneys were grossly normal, except that the cortices were strikingly pallid. Necrosis of the convoluted tubules was present in the deeper cortex. The process appeared to involve principally the proximal convolutions and less extensively the distal convolutions and loops of Henle; the collecting tubules were spared. The necrotic epithelial cells were brightly eosinophilic and contained either pyknotic nuclei or none at all. The brush borders of the cells were obliterated, and the lumina contained a light precipitate of eosinophilic material. In the distal convolutions the greatest change was in the nuclei, which were pyknotic. Desquamated cells extended into the loops of Henle. A zone of subcapsular sparing, 3 to 4 glomeruli in thickness, was present in the superficial cortex. The glomeruli and the intralobular vessels were moderately congested with blood, and there was slight interstitial edema. The pancreas was grossly normal, but in numerous islets of Langerhans the cells were shrunken and pyknotic. There was karyorrhexis, and many islets contained clusters of deeply eosinophilic, necrotic cells. No alteration was seen in the blood vessels of the islets or the surrounding pancreatic tissue.

Case 2.—A girl was transferred to this hospital at 8 hours of age because of respiratory difficulties. The mother's pregnancy had extended two weeks beyond the expected date of confinement but was otherwise normal. Labor lasted five hours, and delivery was spontaneous. At birth the child's condition seemed to be only fair, but within a short period of time respirations became spasmodic and she developed muscular spasticity. When admitted here she weighed 7 lb. 9 oz. and measured 20 in. in length. She was very drowsy and had a weak cry only after marked stimulation. There were cyanosis, prolonged periods of apnea, and muscular rigidity. The Moro reflex was not pres-

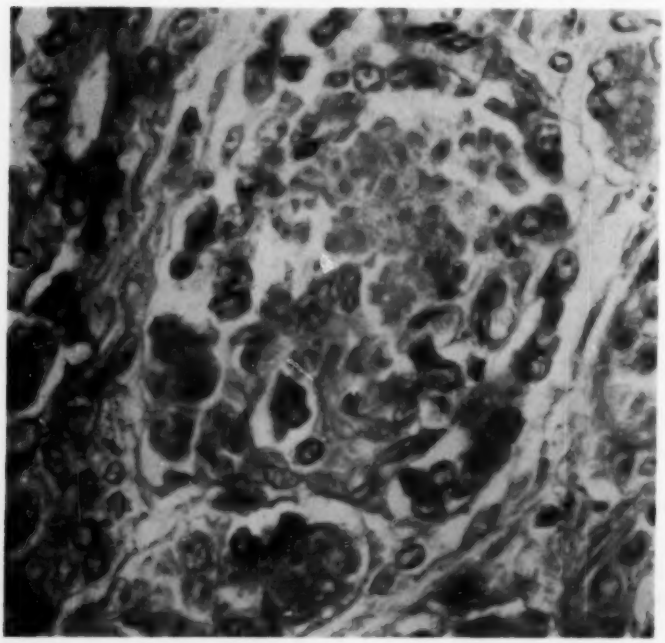

Fig. 1 (Case 1).—Necrotic pancreatic cells represented by cytoplasmic and nuclear outlines. Hematoxylin and eosin; reduced about 15% from mag. × 1060.

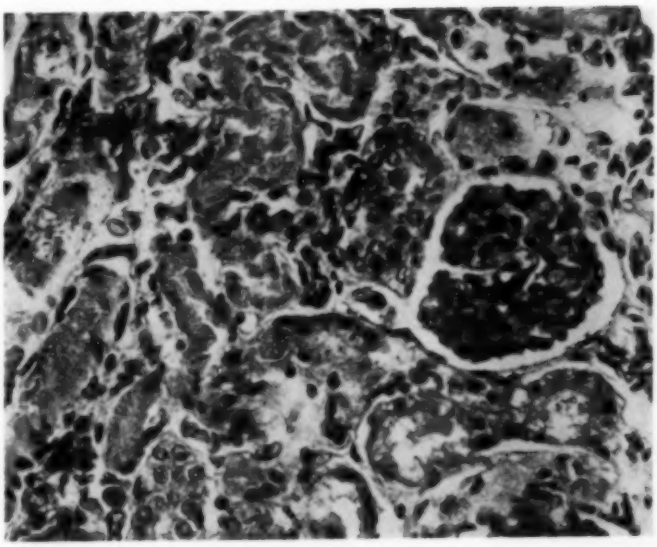

Fig. 2 (Case 2).—The epithelium of the convoluted tubules is necrotic and partially desquamated into the tubular lumina. Hematoxylin and eosin; reduced about 30% from mag. × 660.

ent. Her temperature was normal on admission but momentarily fell to 95 F. A roentgenogram showed limited aeration of the lungs. Despite supportive measures she developed twitching movements and more respiratory distress, dying nine hours after admission.

At postmortem examination, evidence of asphyxia included aspiration of amniotic sac contents, esophageal erosion, slight fatty infiltration of the liver, and numerous perivascular hemorrhages in the brain. The kidneys were grossly normal, and both the cortices and medullae were congested. The microscopic appearance was identical to that in the previous case, except that there appeared to be severer involvement of the loops of Henle and distal convolutions. A thin zone of subcapsular sparing, approximately 2 glomeruli in thickness, was present in the superficial cortex, and the glomeruli and medullary vessels were congested with blood. The pancreas was grossly normal, but microscopically there was partial or complete necrosis of innumerable islets of Langerhans. The acinar tissue and blood vessels were normal.

Case 3.—A girl was transferred to this hospital at the age of 3 hours because of a previous maternal history of Rh sensitization. One sibling was 9 years old and suffered from the sequelae of kernicterus, and another sibling had been unsuccessfully treated for erythroblastosis fetalis seven years previously. This child was delivered one month prematurely by cesarean section, partly because of placenta previa, and she weighed 5 lb. 12 oz. at birth. Laboratory data at 10 minutes of age included a hemoglobin of 15.1 gm. %, a white blood cell count of 49,800 per cubic millimeter, with a differential count of 42% neutrophils, 56% lymphocytes, and 2% monocytes, and a nucleated red blood cell count of 114 per 100 white blood cells. The Coombs test was reported as negative.

On admission to this hospital she was pale and sluggish and had a high-pitched cry. The hemoglobin was 14 gm. %; the red blood cell count 5,020,000 per cubic millimeter, and the white blood cell count, 37,000 per cubic millimeter, with a differential count of 47% neutrophils, 46% lymphocytes, 5% monocytes, and 2% eosinophils. There were approximately 72 nucleated red blood cells per 100 white cells. The direct-acting bilirubin was 0.1 mg. %, and the total, 1.0 mg. %. The baby's blood type was O, CDe, and the mother's, O, cde; the Coombs test was 3+. Shortly after admission the child's color became ashen. Her temperature was normal, but it fell shortly before death to 96 F. Respirations were irregular but not labored, and the rate was 40 per minute. The child developed convulsions and became limp. The Moro reflex was not present, and the liver became progressively enlarged. The hemoglobin level was measured again and was 14 gm. %; the total serum bilirubin rose to only 1.7 mg. %. The child developed respiratory distress and died 11½ hours after admission.

Postmortem evidence of asphyxia included severe pulmonary hemorrhage and petechial hemorrhages in the heart, brain, and intestines. Very slight centrolobular necrosis was present in the liver, and there was focal necrosis in the fetal adrenal cortex. The spleen and liver were not significantly enlarged, and aside from extramedullary hematopoiesis there was little anatomic evidence of erythroblastosis fetalis. The kidneys and pancreas

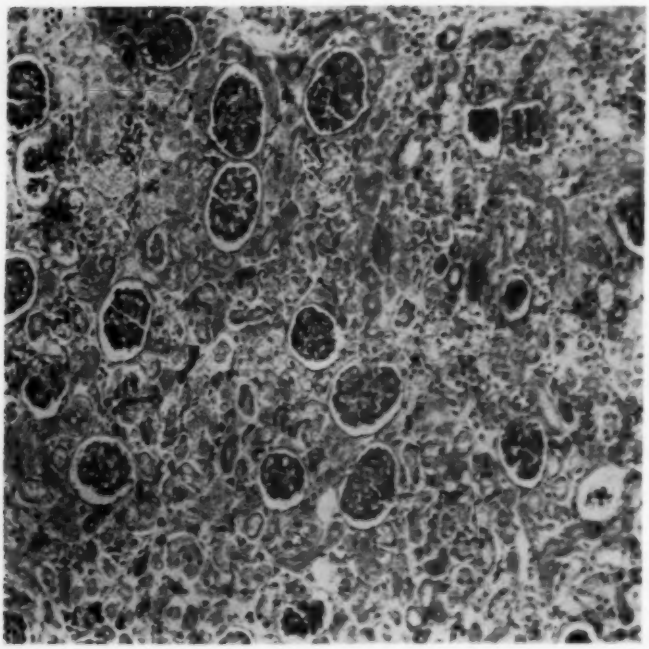

Fig. 3 (Case 3).—The epithelium of the convoluted tubules is necrotic. The superficial cortex is partially spared; glomeruli are normal. Hematoxylin and eosin; reduced about 15% from mag. × 216.

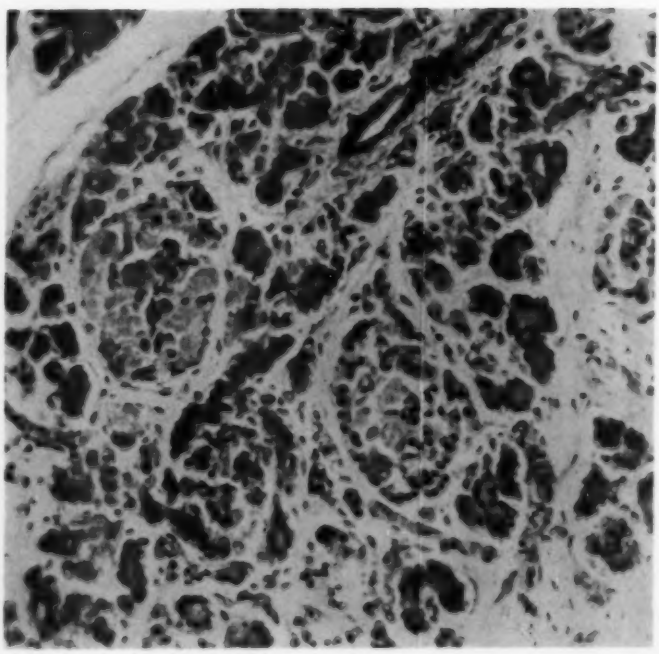

Fig. 4 (Case 3).—Partial necrosis of two pancreatic islets. Hematoxylin and eosin; reduced about 15% from mag. × 300.

were grossly normal, but both presented microscopic lesions identical to those already described.

Comment

In recapitulation, the pathologic finding was selective necrosis, almost coagulative in type, of the renal tubular epithelium and pancreatic islet cells. In the latter there was no distinction between islet-cell types. The process seemed to affect the renal tubular epithelium earlier and more severely than the islet cells. In the case of one child, not presented in this report, there were only eosinophilia and nuclear pyknosis of tubular epithelial cells in the deeper cortex, and the pancreatic islets were histologically normal; this child had lived only seven and one-half hours. From this mild alteration, the lesion seemed to progress through nuclear rhexis and lysis, with increasing cytoplasmic eosinophilia, to desquamation of the cells into the tubular lumina. The pancreatic lesion followed an analogous course.

The necrosis was completely bland, and in the kidney it bore some resemblance to sublimate poisoning. The tubules were not ruptured; there was no abnormal pigmentation, and aside from congestion the blood vessels were normal. Fibrinous exudation could not be demonstrated in the necrotic pancreatic islets, and there was no abnormality of glycogenation. The sparing of tubules in the superficial renal cortex suggested that ischemia was at least a contributory factor. The involvement of both proximal and distal convolutions and the loops of Henle would also favor a circulatory disturbance, but the lesion seemed to involve the proximal convolution to the greatest extent. Were some toxic substance, such as mercury bichloride, responsible there would be a vascular component in the pathogenesis of the lesion.[10] However, there was no evidence in either the material or in the neonatal histories to suggest poisoning.

Necrosis of the pancreatic islets has little association, either observed or postulated, with acute renal tubular lesions. Von Glahn [11] has described similar islet lesions in cases of renal insufficiency, but it is doubtful that these infants became uremic in so short a period of time. Islet-cell necrosis may occasionally be seen in cases of severe hyperbilirubinemia,[12] usually in conjunction with kernicterus and parenchymal necrobiosis in other viscera, but none of the children herein reported was jaundiced.

A search for factors common to the three cases produced two leads. The first was that the renal lesion bears some resemblance to changes we have seen in several older infants, usually suffering from diarrhea and dehydration, who have been treated with sulfadiazine. Each of these three infants received one subcutaneous injection of 5% sulfadiazine sodium, in amounts of 3, 4, and 2 cc., respectively. The dosage cannot be regarded as excessive, and this explanation has been rejected. The second was that all three children suffered from asphyxia. One child was delivered with difficulty after a long labor, and another was delivered by cesarean section because of placenta previa. The condition of all three children after birth was poor; all three had clinical evidence of central nervous system damage, and two suffered from respiratory distress. The children died of asphyxia neonatorum rather than a specific renal, pancreatic, or cerebral lesion.

If related to anoxia and neonatal asphyxia, these lesions, either singly or in combination, must be uncommon complications. Gruenwald, in a survey of asphyxia neonatorum,[13] reported one case of hemorrhagic pancreatitis. In the same series of 500 newborns he found no significant renal lesions and did not describe alterations limited to the islets of Langerhans in the pancreas. (In our own series, approximately one-fourth, or 750 of the autopsies were performed on children who were 2 to 3 days old or less.) No direct evidence can be adduced to ascribe these lesions to asphyxia, but the presence of vascular congestion, the occurrence of anoxic lesions in other organs, and the distribution of the necrosis in the kidney favor that view.

The functional significance of the pathologic alterations cannot be clarified in these three cases. Data concerning renal function are not available, and the children died so soon after birth that there was nothing to arouse clinical curiosity. On the other hand, the natural history of the pathologic changes and their fate remains only partially known. We have not been able to recognize in older children healing stages of the same lesions, and it cannot be asserted that these abnormalities necessarily underlie the functional derangements described by others.

Summary

Three cases of renal tubular and pancreatic islet necrosis occurred in newly born infants who survived one day or less. Circumstantial evidence favors an asphyxial etiology.

Mr. Charles S. Zinser provided the photomicrographs.

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Coarctation of the Aorta

The Syndrome of Necrotizing Arteritis of the Small Intestine Following Surgical Therapy

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The surgical therapy of coarctation of the aorta consists of resection of the narrowed segment and reestablishment of continuity of the vessel by end-to-end anastomosis or the insertion of a graft. Certain complications may be expected because of the nature of the surgery: hemorrhage, aneurysm formation, rupture of the anastomosis, infection. Another, which is due primarily to the success of the operation, is a peculiar obstruction in the network of small vessels supplying the lower body organs. The peripheral manifestations relate chiefly to involvement of the intestine, and it is with these that this communication is concerned.

Report of Cases

CASE 1.—A boy, aged 5, was admitted to Hahnemann Hospital on June 5, 1950. Two months earlier a diagnosis of coarctation of the aorta had been made. There had been no symptoms.

On physical examination the carotid arteries pulsated prominently. There was slight enlargement of the heart to the left. No thrill was palpable. The second sound at the base to the right and left of the sternum was normal. In the third and fourth left interspaces near the sternal border was a loud harsh systolic murmur which was transmitted over the left chest. In the right second interspace was a systolic murmur which was of higher pitch. Radial artery pulsations were normal; no pulsations could be felt in the lower extremities. Blood pressure in the arms was 156/110; it could not be measured in the legs.

Laboratory Data.—The electrocardiogram showed left axis deviation and no evidence of left ventricular hypertrophy. On films and fluoroscopy the significant abnormalities were widening of the ascending aorta and erosion of the inferior border of the right 10th rib. Thoracic aortography demonstrated dilatation of the ascending and transverse portions of the aorta and of the left subclavian artery. Just distal to the origin of the latter vessel was a short area of marked coarctation. There was no postcoarctation dilatation. Collateral vessels were of moderate prominence.

Hospital Course.—Diagnoses of coarctation of the aorta and associated stenosis of the aortic valve or subvalvular obstruction to aortic flow were made. On June 11 the child was operated upon by Dr. C. P. Bailey. The area of coarctation was excised, and an end-to-end anastomosis was accomplished without difficulty. The diameter of the lumen of the excised segment in its narrowest portion was 1 mm. The duration of the procedure was approximately 3¼ hours, and the aorta was clamped for 45 minutes. Four hundred cubic centimeters of blood was given. The blood pressure in the arms after skin closure was 120/90. It was 132/112 in the legs.

Fluid by mouth was allowed as soon as requested, and intake of solid food was started on the first postoperative day. During the next day there were no unusual developments. The blood pressure in the arms rose to 140/98 and remained at this level. On the third day the boy began to complain of abdominal discomfort and his abdomen became markedly distended. Peristaltic sounds were normal at some times and absent at others. Oral intake was discontinued, and Wangensteen drainage, instituted. Thereafter the distention gradually became less marked and the child became more comfortable. After three days the tube was removed. He had three bowel movements the next day and one on the day following. Slight distention was present. No abdominal signs were found during the subsequent 72 hours. However, he then complained of peri-umbilical pain and passed a stool containing a small amount of bright red blood. Several hours later tenderness and muscle spasm were obvious for the first time, confined to the right lower quadrant. The leukocyte count had risen to 27,000 (previously it had not been

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over 12,000), and the temperature rose from 99 F to 104 F.

Laparotomy was now decided upon. When the intestine was exposed, it was found that there were multiple areas of dark discoloration in the terminal ileum and marked mesenteric adenitis. Those areas in the involved segment which were not dark were markedly injected. Sixty-five centimeters of the small intestine was resected, and an end-to-end anastomosis was completed. Thereafter the child's course was satisfactory, and he was discharged 12 days later. At that time the blood pressure in the arms was 130/90.

Prior to the initial operation a diagnosis of aortic stenosis, in addition to coarctation of the aorta, had been made. A six-year follow-up has made it obvious that this diagnosis was correct. He now has a loud, harsh systolic murmur in the second and third right interspaces, transmitted to the neck vessels. A systolic thrill is present in the same area. The electrocardiogram is unchanged. There have been no further signs referable to the original coarctation or to its relief. The blood pressure in the arms is 110/60; in the legs it is 136/100.

CASE 2.—A boy, aged 10, was found to have coarctation of the aorta five months prior to admission. There had been no symptoms.

On physical examination he was found to be rather small. The heart was somewhat enlarged to the left, and the apical impulse was forceful. There was no thrill. The second sound at the base to the left of the sternum was accentuated 1+. A short, rather harsh, moderately loud systolic murmur was audible in the second left interspace and over the neck vessels. At the apex was a systolic murmur of higher pitch. Arterial pulsations in the arms were vigorous; femoral pulsations were absent. Blood pressure in the arms was 174/98. It was not measurable in the legs. Brachial artery pressure, measured directly by cannulation, was 210/132.

Laboratory Data.—The electrocardiogram showed an rsR′ configuration in Leads V_4R and V_1. On films and fluoroscopy the heart and great vessels appeared normal. There was no notching of the ribs. Thoracic aortography demonstrated dilatation of the ascending and transverse portions of the aortic arch and of the left subclavian artery. About 1.5 cm. distal to the origin of the latter vessel was an area of marked coarctation. There was a moderate degree of postcoarctation dilatation. Collateral vessels were not prominent.

Hospital Course.—Resection of the area of coarctation was carried out without difficulty by Dr. H. T. Nichols. An end-to-end anastomosis established an unobstructed lumen. The smallest diameter of the lumen in the excised segment was 2 mm. The duration of the procedure was 3¼ hours. The aorta was clamped for 40 minutes. Five hundred cubic centimeters of blood was given.

On initial examination postoperatively the blood pressure in the arms was 140/100. Arterial pulsations in the legs were very strong. Within a few hours the pressure in the arms rose to 156/120 and remained at a high level for several days, the systolic ranging between 150 and 176 and the diastolic, between 120 and 138.

Fluid by mouth was given upon request, and solid food was given on the second day. On the fourth day the patient began to complain of abdominal discomfort. Some relief was afforded by an enema. Similar complaint was offered from time to time during the next five days. Slight distention was now and again present. Early in the morning of the 10th day the discomfort became severe and there were three episodes of vomiting. A leukocyte count at 9 a. m. was 44,000. Previously it had not been remarkable. By midmorning there was a rise to 52,000. Immediate repeat was reported as 80,000. In each there were 90% polymorphonuclear cells. At midday there was some lethargy. Moderate soft distention was present, and the skin over the abdomen was reddened. As the day progressed the child appeared more and more toxic. At no time was there a rise in temperature.

The decision was made that the abdomen must be explored, and arrangements for laparotomy were completed. It was only after this step that, for the first time, tenderness and spasm, localized in the right lower quadrant, appeared. Previously the abdomen had been soft and nontender. Even now the signs were not striking.

When the intestine was exposed, the same condition existing in Case 1 was apparent. Lymph node involvement was less marked. One hundred twenty centimeters of ileum and jejunum was resected. Side-to-side continuity of the intestine was established.

The postoperative course was satisfactory, there being no further signs of intra-abdominal disorder. The blood pressure in the arms fell to 130/100.

Two months postoperatively the patient's activities were reported to be normal. No murmur could be heard. Blood pressure: arms 102/76; legs 122/70.

CASE 3.—A boy, aged 11, was recognized to have a cardiovascular anomaly at the age of 6 weeks, when a murmur was heard. As he grew older, the parents noted that his exercise tolerance was not normal, although the decrease was not of sufficient magnitude to be cause for concern.

On physical examination the child was thin and underdeveloped. Marked systolic pulsations of the carotids were visible. The heart was enlarged to

the left and downward. The second sound at the base to the left and right of the sternum was somewhat accentuated. A loud, harsh systolic murmur was best heard in the third, fourth, and fifth left and the second and third right interspaces along the sternal border. A loud blowing early-to-middiastolic murmur was well heard in the same area. Both murmurs were transmitted over the entire chest and to the neck. Femoral pulsations were absent. Blood pressure: right arm 150/70; left arm 160/60; legs, unobtainable.

Laboratory Data.—The electrocardiogram showed left ventricular hypertrophy. On films and fluoroscopy the pertinent observations were moderate enlargement of the heart to the left, prominence of the ascending aorta, and notching of the inferior borders of several ribs. Thoracic aortography demonstrated a short area of severe coarctation of the aorta just distal to the origin of the left subclavian artery. There was regurgitation of a small amount of the contrast medium into the left ventricle. Right brachial artery pressure, measured directly, was 200/90. The pulse contour was abnormal, there being an anacrotic dip near the peak and absence of a definite dicrotic incisura.

Hospital Course.—On the basis of the studies, diagnoses of severe coarctation of the aorta and of aortic insufficiency were made. The boy was operated upon by Dr. H. T. Nichols. The area of coarctation was resected, and an end-to-end anastomosis was completed. The smallest diameter of the lumen of the excised segment was 1 mm. The pericardium was then opened, and the heart and ascending aorta were carefully palpated. A faint systolic thrill and a more prominent diastolic thrill were felt over the proximal portion of the ascending aorta. A diastolic thrill was felt, also, over the outflow portion of the left ventricle. The chest was then closed, because the aortic stenosis appeared to be of minor importance.

The aorta had been clamped for 45 minutes. Two hundred fifty cubic centimeters of blood was given during the course of operation.

As soon as the aortic clamps were released, the blood pressure in the right arm was 124/80; while the chest was being closed it rose to 150/100. The pressure in the legs was not measured until 24 hours after the completion of the operation; it was then 190/100.

Fluid by mouth was accepted within 10 hours, and soft solids were allowed on the third day. On the fourth day the boy began to complain of "gas pains." His abdomen was soft, but there was slight generalized tenderness. Peristaltic sounds were present but infrequent. The leukocyte count, at this time was 12,000. Preoperatively it had been 6400. The abdominal symptoms and signs continued unchanged over the next five days. During this period the leukocyte count gradually rose to 18,000 and then fell to 12,000. By this time his appetite was satisfactory and he had a spontaneous bowel movement. On the 12th postoperative day the white cell count began to rise again, and on the 14th day it was 24,000. There was now increased abdominal tenderness and absence of peristaltic sounds. In the early afternoon abdominal tenderness became marked and the leukocyte count was 29,000. The temperature was normal.

The abdomen was opened. Mesenteric lymph nodes were found to be markedly enlarged. The midportion of the ileum was dark blue. In some areas it was black. Two small perforations were identified. The affected segment was resected, and end-to-end continuity of the intestine was restored. Portions of the peritoneum, abdominal fascia, muscle, and skin were excised for study.

The postoperative course was uneventful. To the time of abdominal operation the systolic blood pressure in the arms had been 140 to 150 mm. Hg; thereafter it fell, within eight days, to 110 mm. and remained at this level until the patient's discharge.

Microscopic Pathology

Sections from the small intestine of each patient showed an acute necrotizing hemorrhagic process involving the mucosa, submucosa, and often the inner circular muscle of the intestinal wall.

There was a striking change noted in the small arteries and arterioles in all zones, characterized by fibrinoid necrosis and intense neutrophilic infiltration. Most of the vessels were completely necrotic, although in some the disturbance was focal. In many areas adjacent veins were affected by a similar process. Both arteries and veins were surrounded by zones of cells with elongated plump nuclei and small amounts of fibrillar cytoplasm resembling fibroblasts. Numerous eosinophils were noted in the vessel walls in many areas (Figs. 1 to 3).

Sections from the mesentery showed a similar reaction, although it was more focal in nature, often involving only 20% to 50% of the circumference of the vessel. The adipose tissue surrounding the vessels had undergone necrosis and was heavily infiltrated by neutrophils, eosinophils, and mononuclear phagocytes. There was fibroblastic proliferation in the perivascular zone similar to that in the intestine.

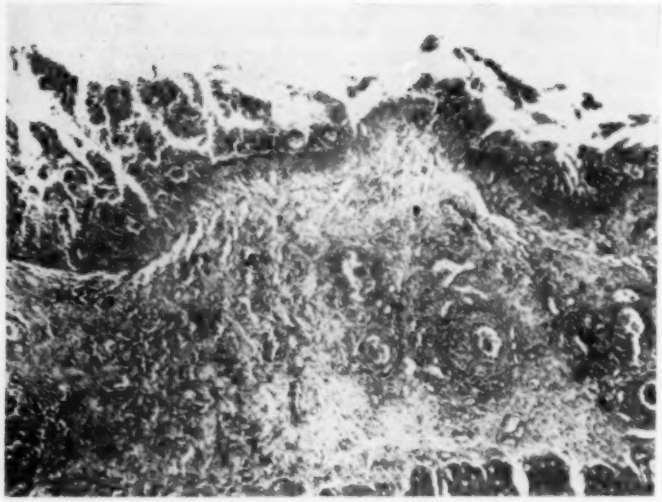

Fig. 1.—Small intestine, revealing necrotic sloughing of mucosa, necrosis of muscularis mucosa, and widening of submucosal zone, with heavy leukocytic infiltration, edema, and necrotizing vasculitis. Reduced about 34% from mag. × 3.5.

There was marked dilatation of the sinuses of the mesenteric nodes, with increased number of neutrophils and some mononuclear phagocytes present within. The follicles presented prominent hyperplastic germinal centers.

In sections from the skin, fascia, and abdominal musculature of the third patient the small arteries in some areas were found to be the site of an extensive cellular infiltrate, predominantly neutrophilic, so dense as to obscure the architecture of the wall.

Cases from the Literature

We have found, in a limited survey of papers relating to coarctation of the aorta, accounts of six patients in whom this complication has been proven.

Sealy [1] reported one in 1953. Later, in 1956, Benson and Sealy [2] presented another and reviewed the history of the first. He was 22 years old, and an area of severe coarctation had been resected. On the third postoperative day he began to complain of abdominal pain. This continued with vary-

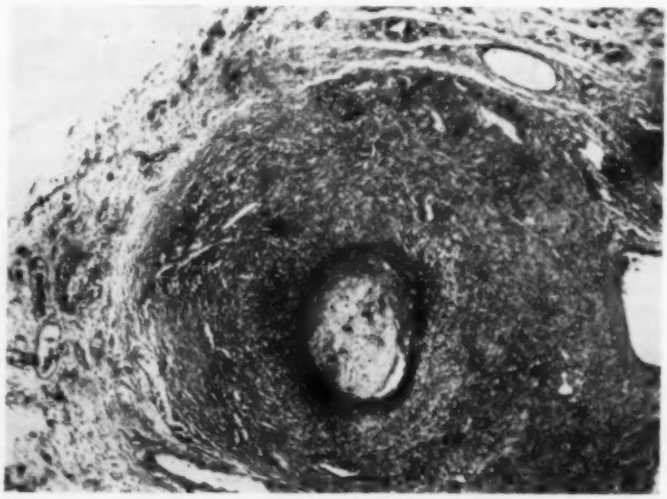

Fig. 2.—Smaller mesenteric artery, revealing diffuse necrotizing arteritis with beginning thrombus formation. Reduced about 34% from mag. × 3.5.

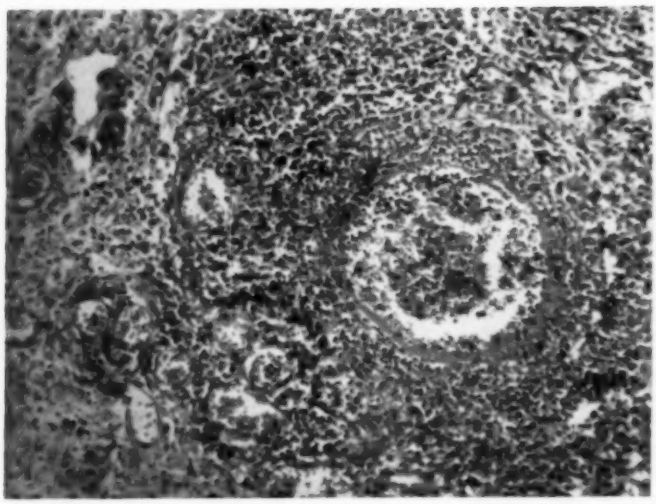

Fig. 3.—Smaller artery, revealing higher-power view of diffuse necrotizing process. Heavy infiltration of wall and adventitia with neutrophils, occasional lymphocytes, and plasma cells. Fibrinoid necrosis of inner muscular wall. Reduced about 34% from mag. × 100.

ing degrees of severity. Initially it was intense and localized in the left lower quadrant. Later it was generalized. Little relief was afforded by various analgesics. On the ninth day his abdomen became distended. During this period of disturbance he had continued an oral intake of fluid and soft food. His temperature, except for a single elevation to 101.3 F, was recorded as 98.6 F to 99.7 F throughout the course. On the day of death it rose to 101.1 F and there was an episode of hematemesis. The abdomen became distended, and peristaltic sounds were absent. Laparotomy revealed infarction of most of the small intestine and the proximal portion of the colon. Cardiac arrest occurred during the final stages of the operation.

Their other patient was a 4-year-old boy whose aortic obstruction was complete. On the third postoperative day he, too, complained of abdominal pain. His belly was soft and nontender. The complaint persisted, and on the ninth day there was some distention. On the 14th day he became fretful and lethargic. Two days later the pain was severer and was localized in the right lower quadrant. On exploration of the abdomen gangrene of the terminal ileum was found and 24 in. of bowel was resected. He survived.

Lober and Lillehei [3] contributed two cases in 1954. The first was a 12-year-old boy who on the fourth postoperative day began to complain of diffuse epigastric pain. On the eighth day his abdomen became distended. Seven days later signs of shock appeared. Abdominal exploration revealed rupture of an aneurysm of the splenic artery and nonviability of a large section of the small bowel. Excision of the aneurysm, splenectomy, and resection of the affected portion of intestine followed. Eight days later the child died.

The second was also a male, a man aged 46.* On the eighth day after coarctation resection his temperature rose and he vomited once. Two days later his abdomen was distended, rigid, and tender. At operation pus was found in the cavity and there were gangrenous patches along the ileum and the distal portions of the jejunum. Proper resection was followed by recovery.

The patient of Perez-Alvarez and Oudkerk [5] was a 5-year-old boy. His postoperative course was uneventful until the eighth day, when he suffered vague abdominal distress. By the 10th day there was severe pain localized in the umbilical region. Exploration on the next day allowed a diag-

* Reported as Case 2 by Ring and Lewis.[4]

nosis of mesenteric adenitis. The pain persisted, and five days later his stools became "tarry." The abdomen was again entered on the 20th day after aortic resection. Gangrene and infarction of one-half of the ileum were now apparent. In one segment there were several areas of perforation. Partial bowel resection was undertaken, but the patient died.

An 8-year-old boy with the syndrome has been reported by Grow, Demong, and Rundles.[6] On the fifth day after resection abdominal pain appeared. There was slight abdominal distention and mild diffuse abdominal tenderness. The temperature was 101 F, and the leukocytes numbered 20,000, with 84% polymorphonuclear forms. The symptoms persisted, although the patient continued to eat and drink small amounts and had bowel movements. On the 19th postoperative day the distention and tenderness had increased and laparotomy was performed. Hundreds of small areas of gangrene, involving almost the entire small intestine, were found. Many had perforated. All of the small bowel, except for 2 in. distal to the ligament of Treitz and 2 in. proximal to the cecum, was resected. The postoperative course was marked by diarrhea, progressive weight loss, and wound dehiscence. The boy died on the 69th hospital day.

In all these persons the basic pathologic process in the bowel was found to be the same, although varying in extent. Necrotizing arteritis was demonstrated, as in our patients. In one patient [3] changes in addition to those in the intestinal vessels were found in the mesenteric, hepatic, and intercostal arteries. In another,[5] similar alteration was present in the bladder, adrenals, kidneys, and renal pelvis. A third [2] exhibited aspects of the disorder in the diaphragm, spleen, kidney, stomach, pancreas, and muscle of the abdominal wall. Biopsy specimens of the structures of the abdominal wall in our Case 3 showed the same process.

Comment

Of obvious importance in the genesis of the pathologic changes is the increase in blood pressure in an area in which preoperatively the pressure had been low. This would involve all tissue below the site of obstruction.

In an attempt to define the mechanism we have reviewed our own series of patients in whom coarctation was relieved as well as those of many others reported in the past. Two facts appear to be significant. Both relate to change in blood pressure following operation. As a rule, in our patients there was an abrupt drop to a normal or near-normal pressure as soon as the aortic clamps were released. The determinations were made by the anesthesiologist while the patient was still in the operating room. In certain instances they were verified by one of us. Within a short period of time—in some cases before the chest was closed and in others before the patients left the operating room—there was demonstrated a rise toward the preoperative pressure level. Hypertension then persisted for days, weeks, or months.

The first observation—the immediate drop in pressure—is supported, unfortunately, by few figures in the literature. The fact of persistence of hypertension of varying duration postoperatively has been known for many years.

One may speculate that the initial fall in pressure in the upper extremities is due to decrease in resistance consequent upon removal of the obstruction. There is now allowed a normal flow of blood under normal pressure into the descending aorta and its branches. Heretofore the flow, whether normal or decreased, was supplied at a low pressure. The small vessels of the intestine and other abdominal organs must suddenly accept, if not a greater load of blood, one presented with greater force. Conditioned by their previously lighter responsibilities, these vessels cannot cope with the situation without change. Or they must change to protect the tissue for which they are re-

sponsible from the effects of sudden alteration in blood supply. In either event, the expected vascular response would appear to be spasm. The narrowed lumina of the arterioles now furnish a resistance to replace blood lost when the coarctation was resected. The blood pressure rises in reflection of this.

So far, this reasoning seems valid in explanation of the persistence of hypertension following successful operation. The hypertension must be due to abnormal resistance at some site. It cannot be the original one, because that no longer exists. It cannot be at the arteriolar level in the portion of the body proximal to the anastomosis, because operation has removed rather than produced noxious stimuli in the region. It is not likely to be of renal origin, because there comes to mind no physiologic mechanism whereby this would be expected and because the original hypertension is so conveniently explained on simple mechanical grounds. Dismissing these possibilities, the logical area wherein we may assume the new resistance to exist is in the portion of the body where the most significant hemodynamic change has been brought about.

Why does necrotizing arteritis develop? Speculation and much experimental work [2] furnish what seems, at the moment, to be a partial answer. It develops as a result of the hypertension. The mechanism is not clear.

Although all tissues distal to the area of coarctation are affected, the small bowel suffers the greatest damage, probably because it is a thin-walled organ and its vessels are not protected by a mass of surrounding tissue.

Recognition and Treatment

In the present state of our knowledge the complication can be expected in any patient undergoing resection of coarctation of the aorta. Indeed, the process probably occurs to some degree in a large number of these persons. Ring and Lewis [4] have pointed out the frequent occurrence of abdominal pain and distention following the operation. Perez-Alvarez and Oudkerk [5] mentioned one person who had abdominal distress greater than would be expected following surgery alone. Claggett and Jampolis [7] made note of a patient who suffered sudden severe burning epigastric pain on the 9th, 10th, and 12th postoperative days. Grow, Demong, and Rundles [6] gave account, in addition to the one above, of six patients who had abdominal pain after operation. One (Case 4) was subjected to laparotomy on the third day because of a suspicion of acute appendicitis. There was a considerable amount of thin free peritoneal fluid. The mesenteric nodes were enlarged. No evidence of panarteritis was found in the resected appendix. Cleland, Counihan, Goodwin, and Steiner [8] reported five patients whose postoperative abdominal pain was severe enough to cause concern. In one the pain was accompanied by massive ascitic effusion. After removal of 2 liters of clear fluid the pain disappeared. These authors report a personal communication from Price Thomas, whose patient developed signs which demanded laparotomy. He found a little free fluid, mesenteric adenitis, and marked enlargement of the mesenteric vessels. In our own series we had previously remarked that the patient who has undergone coarctation resection may complain of abdominal distress for several days while one who has been operated upon for some other cardiovascular lesion will have discomfort for only a few days.

If many patients do have the complication, how may we recognize the ones in whom severe effects on the intestine will develop? How should they be treated? What criteria should we use for laparotomy? Unfortunately, the answers to these questions are unknown. In the light cast by our experience and that of the few who have reported similar cases, we have concluded that in every patient in whom resection of a constricted portion of the aorta is contemplated the possibility must be kept in mind. In discussing with the patient or the parents the mortality and morbidity this complication

should be mentioned. After operation respectful attention must be given all complaints referable to the abdomen. It should be examined daily for evidence of distention or tenderness, even if there are no complaints. A daily count of the leukocytes should be instituted on the first postoperative day. A rising level should cause one to spend more and more time at the bedside, and the determination should be made at increasingly shorter intervals. If the patient begins to show signs of toxicity or develops local or generalized abdominal tenderness, laparotomy is in order.

These suggestions are made with the awareness that to follow them might mean unnecessary operation in some cases. More important, in others, laparotomy may reveal only mesenteric lymphadenitis. The belly will then be closed, and, the physicians responsible having been given a false sense of security, the process may then proceed with an unfortunate termination.

Obviously, prevention of the complication is more important than its therapy. Grow et al.[6] suggest that the use of a Miller-Levin tube to accomplish bowel decompression and of antibiotics to sterilize the intestine are important. It does not seem reasonable that these measures are the answer, because neither intraluminal pressure nor bacterial flora would likely be involved in the genesis or progression of the disturbance. Several colleagues have suggested that antihypertensive drugs should be used routinely to prevent the postoperative rise in pressure in the lower-body segment. This step was advocated, also, in an editorial in *The Lancet*[9] and by Harris et al.,[10] who, because of previously reported experiences,[1, 2] treated three children with postoperative hypertension and progressively severe abdominal pain with these agents. There was "a rapid fall in the hypertension and the abdominal pain, spasm, vomiting and leucocytosis quickly subsided. Recovery was uneventful."

In considering the use of antihypertensive agents one should perhaps give some thought to the possibility that their effect may be as dangerous as the complication itself. If the initial response of the vessels—and we suppose this to be spasm—is protective, might not interference with the process have an unfortunate sequel? The virtue of these drugs must be determined by use, but it is important that a proper degree of caution be exercised.

Summary

A complication of the successful treatment of coarctation of the aorta is necrotizing arteritis of the small vessels in the tissue supplied by the aorta distal to the coarctation. Its incidence is unknown, but in view of the frequency of abdominal pain following operation it probably occurs relatively frequently. The mechanism of its production is uncertain, but undoubtedly the sudden increase in blood pressure is the most prominent factor.

A small number of patients have been reported who have shown severe involvement of the small intestine, leading to the necessity for bowel resection or to death. Three patients who survived the complication are described in the present paper.

From the total experience it is obviously important to pay heed to abdominal signs and symptoms in the hospital period following coarctation resection.

If bowel damage is suspected, prompt operation is in order, with resection of the involved portion of the intestine. The recommendation has been made that antihypertensive drugs be used in those patients with postoperative hypertension and abdominal signs in order to prevent the damage. Although their value must be determined, they should be used with caution, for there may be some element of need for the vascular changes which initiate the hypertension leading to necrotizing arteritis.

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CORRECTION

On page 189 of the August, 1958, issue, the infant food product Similac was referred to as a "low-sodium milk." On page 376 of the September issue, it was referred to as a "low-calcium formula." The manufacturer has pointed out that, although this product is lower in both sodium and calcium content than undiluted whole milk or evaporated milk reconstituted 1:1, it does not warrant either of these categorizations. They emphasize that neither sodium nor calcium has been actively removed during its preparation.

Case Reports

Granuloma Annulare

Report of a Case with Lesions in the Galea Aponeurotica of a Child

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Granuloma annulare is described by Sutton and Sutton [1] as a chronic inflammatory disease of the skin, characterized by deep-seated whitish or pinkish flat-topped nodules which spread peripherally and form circular and crescentic lesions. The sites of predilection are the sides of the fingers and the back of the hand, although the wrists, feet, ankles, neck, elbows, knees, and buttocks may be affected. Subcutaneous lesions appear to be unusual, since these authors call attention to them only through a report by Grauer.[2] Greenbaum,[3] Ormsby and Montgomery,[4] and Allen [5] in their textbooks do not mention the occurrence of the subcutaneous lesions. Pillsbury, Shelley, and Kligman,[6] however, state that rarely are granuloma annulare lesions found only in the subcutaneous tissues. The subcutaneous form was observed on the fingers, the dorsum of the foot, and the forearm in a case reported by Jacobi.[7] He says nothing, however, of their occurrence in the scalp. The scalp as a site of granuloma annulare must be rare indeed, for Little [8] noted but 2 instances of scalp involvement in a review of 49 cases of the cutaneous type. He made no mention of the subcutaneous type. Grauer [2] reported granuloma annulare in a 2-year-old boy in whom approximately six subcutaneous nodules were distributed over the left parietal bone and occiput. They varied in size from a pea to a marble. In addition, the boy had cutaneous lesions which involved the flexor surfaces of the left wrist and the right tibia. Microscopic examination of the tissue from the three sites showed the characteristic picture of granuloma annulare.

Because of the rarity of granuloma annulare as a purely subcutaneous lesion, particularly when located in the scalp, the following case is reported.

Submitted for publication May 1, 1958.

From the Departments of Pediatrics and Pathology of the Albert Einstein Medical Center, Northern Division. Pediatric Resident (Dr. Tuncali).

Report of Case

A 4-year-old boy was admitted to the hospital on Nov. 5, 1957, for study because of a number of swellings located in the scalp of the left frontal bone. According to his mother, the first swelling appeared on the left forehead at about the age of 6 months. It varied in size from time to time and eventually disappeared. Subsequently, however, other swellings appeared which persisted. Since the mother thought the swellings to be due to trauma, she at first paid little attention to them. Later, becoming tumor-conscious, she consulted her physician, who referred the child for a definitive diagnosis.

Family History.—The mother and father are living and well. One brother, aged 11 years, is well. There is no history of tuberculosis, rheumatic fever, rheumatoid arthritis, or allergy in the family. The child was not, as far as could be determined, ever in contact with a case of tuberculosis.

Physical Examination.—The child was a well-nourished and well-developed healthy boy. On the left side of the forehead there were about six hard discrete swellings, distributed in a somewhat irregular linear manner, that extended beyond the hair line. They were fixed and felt as though they were attached to the bone. In fact, the first tactile impression was that of exostoses of the skull. They varied in size from 0.5 to 1.5 cm. They were not tender or painful on palpation nor was any inflammation or induration noted in the overlying freely movable skin. The larger lesions could be seen as smooth rounded swellings under the scalp. Their

presence, however, could be best appreciated by palpation. There was minor enlargement of the cervical lymph nodes. There were no other abnormal findings on complete physical examination. No other skin lesions were present.

The radiological examination of the skull, with particular attention to the left frontal and parietal regions, revealed no evidence of osseous abnormality. There was soft tissue variation in contour, related to the clinical evidence of soft tissue masses.

Laboratory Findings.—A tuberculin test with 0.00002 mg. P. P. D. was negative. ECG, normal; ESR (Wintrobe), 9 mm. in an hour; hemoglobin, 12.6 gm.; hematocrit, 36%; leukocytes, 5500; polymorphonuclear cells, 60%; lymphocytes, 34%; monocytes, 5%; basophils, 1%.

Biopsy.—A definitive clinical diagnosis of the scalp lesions was not made, and so two days after admission biopsy was performed.

An incision was made in the scalp behind the hair line, directly over two of the masses. The incision was deepened through subcutaneous tissue until the deep fascia was incised. The galea aponeurotica was then identified, and within the latter and covered by a thin membrane of this structure were two nodules approximately 0.5 cm. to 1 cm. in diameter. These were excised by dividing the galea widely about them and lifting the entire block of tissue from the skull.

Pathologic Examination of Biopsy Specimen.—Gross: The specimen consisted of three pieces of tissue measuring 0.3, 0.4, and 0.5 cm. in greatest dimension, respectively. They were of irregular outline, pink-gray, and fibrotic.

Fig. 1.—Low-power view of typical stellate granuloma. Hematoxylin and eosin. Reduced about 10% from mag. × 55.

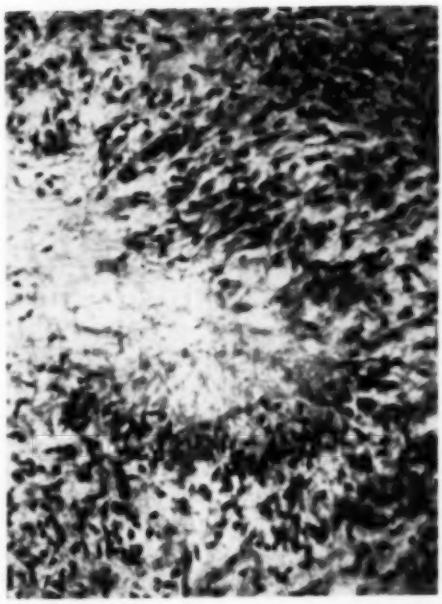

Fig. 2.—High-power view of granuloma with palisaded periphery and necrotic center. Hematoxylin and eosin. Reduced about 10% from mag. × 250.

Microscopic Examination (Figs. 1 and 2): The tissue is made up of a fibrotic matrix of dense collagen consistent with galea aponeurotica. There are occasional loose dispersions of lymphocytes and a general increase in cellularity of the tissue by virtue of histiocytic proliferation. Most prominent are multiple focal lesions of general stellate outline having an average diameter of 250μ. These consist of central areas of necrosis surrounded by a palisaded ring of epithelioid cells. The necrotic center is made up of eosinophilic fibrillary material and is of the coagulation type of necrosis. The outlines of destroyed cells are still visible.

The surrounding cells are large. They have large, usually fusiform nuclei which are hyperchromatic. These nuclei are more hyperchromatic and less finely reticulated than the nuclei of typical epithelioid cells of other granulomata. This ring is multilayered, and the nuclei tend to be oriented toward the center. The cytoplasm tends to be syncytial. There are no associated giant cells.

Differential Diagnosis: The lesion has the histologic appearance of either granuloma annulare or a rheumatoid nodule. The location of the lesion in the galea without involvement of the skin is unusual for granuloma annulare.

Diagnosis: Granulomatous lesion of galea aponeurotica, consistent with granuloma annulare or rheumatoid nodule.

Comment

According to Allen,[5] the histology of the cutaneous lesions of granuloma annulare is identical to that of the rheumatoid nodule.

Jaeger[9] also stated, in a report of one case of necrobiotic nodules (rheumatoid nodules) and two cases of granuloma annulare, that the histologic appearances of the two entities are identical. Bowers,[10] however, distinguishes histologically the lesions of granuloma annulare from rheumatoid nodules. He admits, however, that it may be difficult to do this. He proposed definite histologic criteria to distinguish between the two lesions. These criteria, however, were not helpful in making a histologic distinction in this case. Since the child showed no manifestation of rheumatoid arthritis, it is reasonable to assume that the scalp nodules were granuloma annulare.

Granuloma annulare occurs more commonly in young children and tends to spontaneous involution without scarring. It may remain present for months or years. The etiology is not definitely known. Pillsbury, Shelley, and Kligman[6] think that an unusual response to trauma must be considered. Tuberculosis as an etiological factor in this disease is frequently mentioned in the literature. Little[8] inclined to the belief that the disease was of tuberculous nature. Prunty and Montgomery,[11] however, studied 31 cases in which a tuberculous etiology was carefully investigated. Their observations tended to speak against a tuberculous etiology, since the histological picture certainly was not that of tuberculosis.

Michael,[12] in a report of eight cases and a review of the literature, concluded that there is no evidence favoring a tuberculous origin of granuloma annulare.

On the other hand, Bugarski[13] is of the opinion that granuloma annulare is a photodermatosis in which the tubercle bacillus and its toxins play the role of endogenous photocatalysts. In experiments on 10 cases he showed that all lesions healed completely when the factor of exposure to sun rays was eliminated, while excochleation did not influence them. This justified the conclusion that the alleged favorable influence of excochleation is actually attributable to the protective dressing applied afterward. All his cases gave a positive tuberculin reaction. Bugarski's opinion is difficult to accept, since granuloma annulare occurs in covered parts of the body. Furthermore, there is at present increasing evidence that tuberculous infection is usually not demonstrable in this disease.

The treatment of granuloma annulare has been most unsatisfactory. The many varied therapeutic measures that have been recommended indicate that there is no specific treatment.

Pillsbury, Shelley, and Kligman[6] state that simple infiltration of the area with procaine or incision of the lesion may at times be followed by complete and rapid involution, although this is by no means invariable. They also state that x-rays or Grenz rays have been used with beneficial results but that topical preparations are of no value. Cochrane[14] treated 13 cases of granuloma annulare with a tocopherol (Ephynal) with what seemed to be excellent results.

Electrolysis was used by Hansen[15] in the treatment of 20 cases of granuloma annulare. The lesions disappeared in 18 in the course of about three weeks. In two cases the growths did not recede completely but were improved.

Since spontaneous involution of the lesions of granuloma annulare sometimes occurs, it is always difficult properly to evaluate the results of any treatment of this disease.

From the foregoing it can be appreciated that a decision as to the management of granuloma annulare cannot easily be made. Our patient was discharged to the care of his physician, with the advice that for the time being nothing should be done, in the

expectation that the procedure of biopsy would induce a spontaneous involution. On March 15, 1958, four months after biopsy, he was examined by his physician, Dr. Irving Tenenbaum, of Cape May, N. J., who submitted the following report: "The lesions in the scalp are no longer seen on inspection. They still can be palpated, however, but are about one quarter their previous size."

Summary

A case of the rare subcutaneous variety of granuloma annulare occurring in an equally rare location, viz., the galea aponeurotica, is reported. A brief review of the literature indicates that the etiology is not known, nor is there any specific therapeutic measure for its eradication.

235 S. 15th St.

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Spastic Quadriplegia Combined with Congenital Ichthyosiform Erythroderma and Oligophrenia

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This report deals with the new syndrome oligophrenia combined with congenital ichthyosiform erythroderma and spastic disorders, first described by Sjögren [1] in 1956. In 1957 Sjögren and Larsson [2] reported on 28 cases of this condition, and, according to these authors, to their knowledge, there is no known instance of this syndrome having been reported in the literature. Söderhjelm and Enell [3] have also published an account of some of these cases. These authors concluded that the disease has a genetic causation and demonstrates the autosomal recessive type of inheritance.

In the course of an investigation into genetic factors pertaining to the etiology of palsy being conducted at The Moody State School for Cerebral Palsied Children a case exhibiting this syndrome was encountered. The apparent rarity of this condition and the localization to Sweden of the affected persons reported so far prompted us to investigate and report this case.

Report of Case

The pedigree presented diagrammatically in the Figure was established by interviewing the mother of the proband, by examination of medical records, and by correspondence with persons concerned with the case. The Roman figures on the left indicate generations, and the Arabic figures locate persons.

A boy was born in the breech position on Nov. 20, 1948, after a normal 8½-month pregnancy and an 18-hour labor. Birth weight was 7 lb. 8 oz. There was no history of cyanosis or jaundice; however, the infant was placed in an incubator for 24 hours. His diet was adequate. Exfoliative dermatitis was present over his entire body with the exception of cheeks, upper portion of hips, and buttocks. The palsied condition was first noted at 8 months of age. He is a spastic quadriplegic. The mother states that the child held up his head at about 10 to 11 months. She described his development before that time as "slow" but not unusual. He was never able to crawl and never walked until he received braces and crutches, in January, 1955. It was noted that the child never perspired except around the nose and that he suffered considerably from the hot weather.

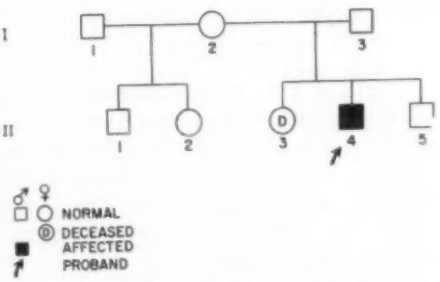

Fig. 1.—A pedigree showing a case of spastic quadriplegia combined with congenital ichthyosiform erythroderma and oligophrenia. Roman numerals on the left identify generations. Arabic numerals indicate persons.

In March, 1953, the patient was given his first intelligence test, the nonlanguage portion of the Merrill-Palmer Pre-School Scale. His physical status precluded the use of other tests. Motor coordination appeared to be poor and could be attributed in part to the spasticity. He showed preference for the right hand but used the left hand more than would normally be expected. The examiner found that generally he functioned at about the 2-year-old level, and his intelligence quotient was estimated to fall between 40 and 50.

In May, 1954, the patient had anterior and posterior obturator nerve crushings. Posterior tibial nerve branches to the gastrocnemic muscle were also crushed. Later that month he was seen for

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Mental Development of Patient

Test Administered	Intelligence Quotient	Mental Age	Chronological Age, Mo.
Merrill-Palmer Pre-School Scale	40-50	30-35 mo. (generally functions at 2 yr. level)	53
Merrill-Palmer Scale with supp. items from Terman Merrill revision of Binet Scale	56-65	36-42 mo.	66
Stanford-Binet, Form L, & Columbia Mental Maturity Scale	45-55	36-44 mo.	80
Binet & Columbia	43-46	38-41 mo.	89
Stanford-Binet revised Form L & full-range picture vocabulary scale	34-38	33-36 mo. (comprehension 2½ to 3 yr.)	95

psychological evaluation. Diagnosis at this time was mental retardation. In July, 1955, when the patient was tested again, he was found to have practically no speech. The examiner picked up only two or three words. All other vocalization sounded like infantile repetition of the "da" sound. Visumotor coordination was impaired because of mental and organic defect. Intellectual functioning was found to be poor. However, it was felt that the validity of the scores was subject to some question, owing to his several handicaps. It was noted that he did better in following simple instructions than he did in expressing himself. Motor coordination was at approximately a 3-year-old level. He was evaluated for speech and hearing in June, 1956. Hearing was normal. Oral examination revealed voluntary protrusion and right lateralization of the tongue. There was reflexive lateralization, both left and right, and elevation. Jaw closure was slow, and the tongue movements were labored and sluggish. Physiological readiness for speech was poor. Social readiness for speech was markedly delayed. The boy was again tested in November, 1956, and showed a great deal of perseverative behavior and rote-type responses that indicated a lack of comprehension beyond the 2½- to 3-year level. He showed poor perception as well as comprehension of the use of objects in his everyday world. His responses beyond the 3-year level were all guesses, without any real comprehension of what was expected from him. Tests administered and findings are recorded in the Table.

In 1957 the patient's eyes were examined and found to be straight; fundus, clear; retina and disc, normal. It was the physician's opinion that the boy could see well with each eye. Chest roentgenograms gave the impression that there may be some cardiac enlargement, especially left ventricular. This may have been more apparent than real because of rotation. The chest was otherwise negative. Roentgenographic examination of the pelvis (anteroposterior and frog-leg position) revealed the bones of the pelvis as normal. The sacroiliac joints were also normal. There was no significant abnormality of the hip joints or upper ends of the femora. The symphysis pubis appeared to be slightly widened. In May, 1957, this boy was diagnosed as having congenital ichthyosiform erythroderma by the dermatology staff of The University of Texas—Medical Branch.

The mother of the proband has two normal children (Figure), II 1 and II 2, by a former marriage. The paternal family of these two children came from Mississippi and Illinois and are said to be descended from Indians. The third child (II 3), the first by her second husband, was also delivered in the breech position and died the second day after birth. When the proband was born the father was 34 years of age and the mother was 27. The youngest sibling (II 5), born May 12, 1952, is apparently normal. The father (I 3) of the proband reports that his family originally came from France. The proband's mother's family came from Wales. The mother is blonde and has very sensitive skin.

Comment

In view of the foregoing family history it is interesting to speculate as to the genetic origin of this syndrome. It is noteworthy that in the series of 28 patients reported by Sjögren and Larsson[2] the parents (with 3 exceptions) were born in the county of Vasterbotten in the north of Sweden. The results of their genealogic and geographic analysis suggest that for the great majority of the patients the recessive gene responsible for this condition had its origin in a single gene mutation which might have occurred as early as the middle of the 14th century, since it was already widespread in the early 18th century along the eastern seaboard of Vasterbotten. The probable heterozygous lines for most of the parents were traced to a fairly restricted area in the northeastern part of the county. Also of interest, as pointed out in *The Lancet*,[4] is the fact that these authors found two affected children of Lapp race. "There is a suggestion here (though Sjögren and Larsson do not make the point and may have reasons against it) that the mutation may have been present in the native inhabitants

before the Swedes themselves intensively colonised the county in the 14th century."[4] It is of course possible that the ancestry of the patient reported here could be traced back to this single gene mutation. However, there is also the possibility that the mutation has occurred more than once and that actually these cases are more numerous than the published number indicates.

We should also like to point out that two of the children, II 3 and the proband, the third and fourth pregnancies by the second marriage, were born in the breech position. It is conceivable that II 3, had she lived, might also have been affected. Indications in our investigative program into genetic factors pertaining to the etiology of cerebral palsy now in progress are that so-called abnormal deliveries among probands and siblings are more prevalent in families with cerebral palsied children.

Summary

A case of oligophrenia combined with congenital ichthyosiform erythroderma and spastic quadriplegia is described. Twenty-eight previously reported cases in the literature of this syndrome were all from Sweden.

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Lipoid Proteinosis

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Although lipoid proteinosis is observed primarily in the child, references to this condition in the pediatric literature are scant. The term lipoid proteinosis was first used by Urbach [4] in 1932. This, however, was the renaming of this group of cases, as they had been previously called lipoidosis cutis et mucosae.[2] In 1924 Wiethe [1] had reported the first of these cases as a disease consisting of skin and mucous membrane involvement, but not until 1929 did Urbach and Wiethe [3] show their cases to be identical. Their patients showed a hoarseness present almost since birth, with growths involving the mucous membranes and vocal cords. Nodules and plaques occurred on the gums, mucous membranes, floor of the mouth, soft palate, frenulum of the tongue, and uvula. Mucous membranes of the genital and rectal areas were similarly affected. Incidental findings reported by other observers included alopecia of the scalp, loss of eyelashes; dental abnormalities, such as aplasia or hypoplasia; calcifications within the skull, and visceral involvement of the pancreas,[3] liver,[8] testes, and parotid gland.[9]

Several workers have found that more than one member of a family may have this disease. This was shown by the two families which were studied by Urbach and Wiethe [3] and the family which was discussed by Wise and Rein.[6] Also, there may be a history of consanguinity in the parents.

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The usual microscopic feature seen in a section of abnormal skin, stained with hematoxylin and eosin, from a patient with lipoid proteinosis is a homogeneous material having a pinkish cast dispersed in the upper dermis and about the smaller blood vessels. Special staining of this material with Sudan IV produces a reddish brown color. Congo red is nonstaining to this material. There are no foam cells present in this disease. The epidermis is affected only secondarily, if at all.[12]

Chemical analysis of the fatty elements of the blood are essentially within the range of normal. Wile and Snow [8] found the fasting blood sugar level to be low and the dextrose-tolerance test to be characterized by a flat curve. Tripp [5] and Montgomery and Havens [7] noted an elevation of the phosphatide fraction of the serum.

The purpose of this report is to record a deviation from the usual clinical findings in patients having lipoid proteinosis. A consistent finding in all previously reported cases to date, in which this child is the exception, is the involvement of the mucous membranes and the pharynx.

Report of Case

The patient is an 11-year-old white girl who was born and has lived in Africa most of her life. Since the age of 4 years there had been areas of thickening of the skin over the forehead, nose, dorsum of the hands and forearms, and about the knees (Figs. 1, 2, and 3). At no time was there any pain or change in sensation. Aside from the usual childhood diseases, her past medical history was not unusual.

On physical examination all findings were within the accepted limits of normal except for the skin. Special attention was given to the mouth and throat examination. The mucous membranes were clear, as were the coverings of the vocal cords. Hoarseness was not present.

Fig. 1.—Lipoid proteinosis, showing plaques and pits on forehead and nose.

Fig. 2.—Lipoid proteinosis, showing plaques on dorsum of hands.

The areas of the skin mentioned above had somewhat-thickened plaques in which the color was slightly yellower than the rest of the child's fair complexion. On the dorsum of the hands were a few recently healed areas which previously had been blisters. The clinical appearance of the child was that of the typical patient with lipoid proteinosis.

Extensive laboratory studies were made. These included urinalysis; blood cell count with differential count; albumin, globulin, and fractional protein studies; and determination of nonprotein nitrogen; liver-function tests included thymol turbidity, cephalin flocculation, cholestrol, prothrombin time, alkaline phosphatase, and serum bilirubin; other studies included electrocardiogram; bone marrow study; culture of materials from nose, throat, urine, and blood; x-ray of chest, long bones, and skull; muscle biopsy studies, and the Congo red test. These were all within the accepted limits of normal.

Examination of a specimen of pathologic skin by microscopy showed the following: The epidermis was normal in all respects. The dermis contained extracellular foreign substance located in the walls of blood vessels and dispersed throughout the upper corium. Differential staining led to the final evaluation of this material being either amyloid or a lipoid protein combination. Congo red stain did not affect this foreign substance, while Sudan IV (Fig. 4) stained the aforementioned material reddish brown, this being the accepted reaction of lipoid protein.

Fig. 3.—Lipoid proteinosis, showing plaques on forearms.

Comment

Chemical studies of tissues from pathologic sites have shown that the material deposited in the skin in lipoid proteinosis is sudanophilic and lipid in character. The lipid material consists of phospholipid or

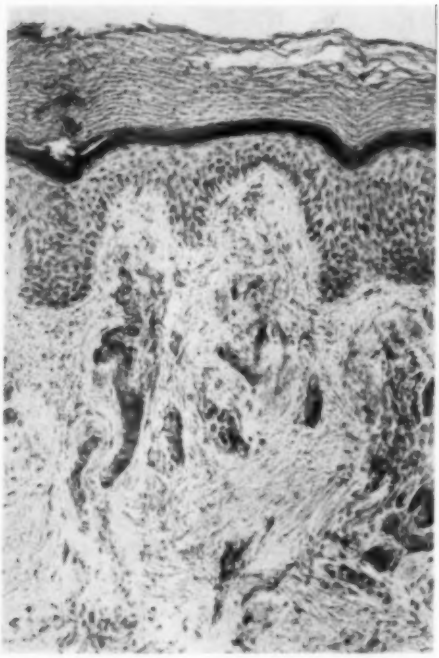

Fig. 4.—Photomicrograph of skin specimen in case of lipoid proteinosis, showing extracellular material in upper corium. Sudan IV stain; reduced about 40% from mag. × 300.

galactolipids.[11] Studies of the abnormal skin by chemical techniques have shown that the concept of lipoid and protein should be enlarged to include polysaccharides along with nonacidic carbohydrates and neutral fats.[13]

The basic defect of metabolism involved in this disease process is not known. However, some contend that "lipoid proteinosis is usually a nevoid, familial disturbance, beginning in infancy and associated with a tendency towards diabetes." [7]

The response to treatment of patients with lipoid proteinosis has not been remarkable. According to a report by Tompkins and Weinstein,[10] lipocaic has been of some help. Surgery has been necessary in cases of severe involvement of the mouth and throat.

Summary

The typical example of lipoid proteinosis with nodules and tumors of the mucous membrane and skin is discussed. The usual histochemical and histopathologic features are reported.

Our patient is free of all mucous membrane involvement, even though the disease process has been present for seven years. She does have the usual involvement of the skin of the face, arms, and legs with yellowish plaques, scars, and recurring blisters.

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Congenital Varicella

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Newborn infants are passively protected against certain viral diseases by transplacental transmission of immune antibodies. Ehrlich,[1] in his study of antitoxin immunity to ricin, showed that passive transfer from immune mothers to their offspring occurs naturally. This transfer has been demonstrated by neutralization tests for poliomyelitis[2] and for influenza, yellow fever, smallpox, and cowpox vaccine.[3] Laboratory tests are not available for the transmission of antibodies for the virus of chickenpox.

Clinical observation suggests that there is transplacental transmission of immune antibodies against varicella. Most mothers have had this disease before they become pregnant. Its occurrence is rare in young infants. The records of Willard Parker Hospital in New York show that among 2200 admissions of patients of all ages for varicella during a three year period there was only 1 case of chickenpox in a newborn infant (0.05%) and only 46 cases in the age group from two weeks to six months (2.15%).

It would seem that the immunity of newborn infants for varicella is dependent on the transfer of maternal antibodies and that they are susceptible to the disease if there is insufficient or no antibody transmission. The histories of the cases of chickenpox in newborn infants reported in the literature reveal that the mothers either had chickenpox during the last two weeks of pregnancy,[4-17] or never had the disease and that older siblings had varicella during this period.[4,5,18] (See Table.)

The incubation time of varicella ranges usually between 10 and 22 days. Therefore only those cases can be considered as ma-

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TABLE.—*Maternally Transmitted Cases of Varicella Reported in Literature*

Year	Author	Cases, No.	Maternal Varicella During Last 2 Weeks of Pregnancy	Mother Never Had Varicella. Chickenpox in Older Siblings 1-2 Weeks Prior to Birth of Infant	Infantile Skin Lesions
1878	Hubbard [4]	1	+	—	1st day
1913	Pridham [5]	1	—	+	At birth
1927	Mitchell [6]	1	—	+	At birth
1934	Henderson [16]	1	+	—	8th day
1934	Cosgrave & Samuel [7]	1	+	—	At birth
1935	Baron [15]	1	+	—	8th day
1939	Mitchell [8]	1	+	—	At birth
1939	Shuman [9]	1	+	—	2d day
1944	Oppenheimer [11]	1	+	—	7th day
1947	Lucchesi et al. [12]	2	+	—	8th day
			+	—	9th day
1948	Caravia [10]	1	+	—	At birth
1953	Middlecamp [11]	2 (Twins)	+	—	At birth
					At birth
1954	Odesky et al. [13]	3	+	—	At birth
			+	—	10 hr. after birth
			+	—	At birth
1956	Waddington [18]	2 (Twins)	+	—	2d day
					8th day

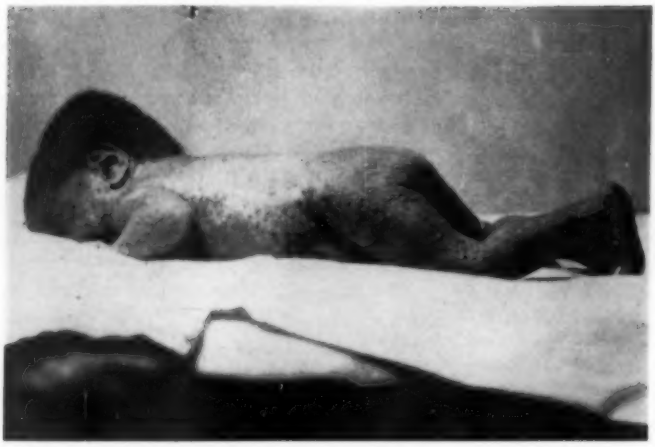

Fig. 1*A*. — Maternally transmitted varicella. All development stages, macules, papules, vesicles, and pustules, seen side by side. Appearance on 5th day of life.

ternally transmitted (congenital) where eruption occurs during the first nine days of life. In infants where the lesions appear 10 to 22 days after birth, there may have been an intrauterine infection, but more probably the disease was contracted from an environmental contact, as demonstrated in the case of Mössmer,[19] where eruption occurred on the 19th day of life. By these criteria there are 14 reports of probable congenital varicella in the literature.[4-17] Three cases were fatal.[12,13,16] Recovery was uneventful in the remainder. The purpose of this report is to present an additional case of maternally transmitted chickenpox.

Report of Case

A 30-year-old Puerto Rican woman had developed crops of pimples and blisters eight days before the termination of her third pregnancy. A diagnosis of typical varicella was made. On the day of admission to the hospital she delivered spontaneously a girl weighing 7 lb. 8 oz. (3402 gm.). At birth the infant seemed completely normal; at 48 hours the temperature rose to 103 F and a small "tear drop" vesicle appeared on the buttock. The infant was transferred from the nursery to the isolation ward. On the third and fourth days successive crops of papules, vesicles, and pustules appeared on face, trunk, and extremities. The content of the older blisters became cloudy, others broke, and scab formation occurred. On the fifth day, the very extensive eruption covered all parts of the body (Fig. 1 *A* & *B*), and there were

Fig. 1*B*. — Maternally transmitted varicella. Appearance on 5th day of life.

many vesicles on the mucous membranes of mouth, throat, and vaginal labia, and on the palpebral conjunctivas. All stages of the eruption from macules and vesicles to pustules and crusts could be observed side by side. The body temperature varied from 102 to 104 F (38.8-40 C). The infant was toxic. The newborn was transferred from Metropolitan Hospital to Willard Parker Hospital. There the baby developed new skin lesions for two more days. On the ninth day, the temperature returned to normal. Within three weeks there were only very few superficial lesions remaining.

The infection did not spread across the original nursery. None of the other newborn infants developed varicella. However, on the isolation ward to which the baby was transferred on the second day and where there had been no case of varicella for three months, a 4-year-old girl and a 7-year-old boy developed the disease 2 weeks and 16 days, respectively after the admission of the infant.

Comment

The differential diagnosis of varicella in the newborn infant includes many disorders. In impetigo the smears and cultures of the vesicle fluid usually reveal staphylococci or streptococci. On culture of vesicle fluid, there was no growth in the case reported. The lesions in variola show only one stage of development, that is, either macules or vesicles or pustules, at one time. Vesicles in smallpox are multichambered. The vesicles in this case emptied their content completely on lancing. There was no case of smallpox in New York City at that time, and the mother had been vaccinated two years prior to the baby's birth. Generalized cowpox vaccinia may produce a similar picture. It is usually seen on eczematous lesions not present in this case. Neither the baby nor anyone in the infant's environment had been vaccinated recently. Severe herpes simplex infection of the skin is characterized by patches consisting of small vesicles surrounded by a hyperemic area which lead to scab formation. This type of eruption could hardly be confused with the eruption in this infant. In pemphigus neonatorum and Ritter's exfoliative dermatitis, the bullas are much larger. The epidermis becomes movable above the corium in so-called normal skin areas, as is evidenced by the Nikosi sign, which was not present in this case. Lesions of the severity seen in this infant are rare in ordinary cases of chickenpox. The only eruption closely resembling this picture is Kaposi's varicelliform eruption, usually a complication of eczema. This condition is, in fact, so similar to varicella that its differentiation by morphology alone is almost impossible.[17]

The diagnosis of congenital varicella in the present case would seem to be confirmed by the maternal history of varicella one week prior to the infant's birth, the appearance of a characteristic eruption 48 hours postnatally, the typical clinical picture, and the fact that two children on the ward to which the baby was transferred, where there had been no other case of chickenpox for three months, developed the disease within the average incubation time. Odessky et al.[12] recommended that all babies in a nursery should be isolated when a case of congenital varicella may be expected from a history of maternal chickenpox within the two last weeks of pregnancy or of chickenpox in older siblings during this period of time. However, cross infection is unlikely, owing to natural immunity of the other infants.

Summary

A case of maternally transmitted (congenital) varicella has been presented and compared with 14 previously reported cases.

The differential diagnosis of varicella in the newborn infant is considered.

It is thought that isolation of newborn babies born from mothers who had varicella during the last two weeks of pregnancy may be indicated.

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Myocarditis in Infancy with Inclusions Characteristic of Psittacosis

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Recently, there has been an increased interest in myocarditis during infancy. Conlin and Mantz [1] reported 26 cases up to 1953. Saphir [2] states that since 1953 he has collected 29 cases in the American literature and 39 cases in the foreign literature. He reported an autopsy series of 5 cases in 1957 which were added to 11 cases already in his material up to 1952. The clinical findings are well described by several authors, including Rosenbaum [3] and Tedeschi.[4] There is usually a sudden onset of heart failure in a child under 2 years of age. Physical examination reveals marked tachycardia with an enlarged heart. Nonspecific electrocardiographic changes associated with cardiac hypertrophy and damage are described. Autopsy findings reveal an enlarged dilated heart with congested lungs. Inflammatory cells are found in the interstitial tissue of the myocardium separating muscle fibers which are necrotic. Saphir states that foci of inflammatory cells are also present in the endocardium and pericardium. An incidence of pneumonitis, hepatitis, and meningoencephalitis occurring with this process is reported, indicating that the disease may be a generalized one primarily manifested by myocarditis. The etiology is unknown, but viruses are strongly considered because of the similarity to the myocarditis associated with proven viral diseases such as poliomyelitis, Coxsackie disease,[5] and influenza. Because the diagnosis is usually not made until the histologic sections are returned, Saphir states, virus studies on clinical autopsy cases are not available. Unfortunately, this is also the case concerning this presentation.

As is well known, the psittacosis agent comprises a group of organisms of many different strains, having common morphologic and antigenic similarities and occupying a position intermediate between viruses and Rickettsia. Clinically, pneumonitis usually results. Other organs, however, are affected, such as brain, liver, spleen, and heart.[6-8] Levinthal, who gave his name to the inclusion bodies, described them in experimental animals with pericarditis and hypertrophy.[9] Histologically, the pneumonitis is very characteristic, being composed of macrophages and monocytes, with hyperplasia of the alveolar lining cells. There is only slight infiltration of the alveolar septa, with little or no change in the bronchi and bronchioles.[8,10] Characteristic Levinthal-Cole-Lillie bodies are seen in macrophage-type cells.[8,9,11] These inclusion bodies are easily demonstrated tinctorially by basic dyes and are seen under the light microscope, varying from 0.3μ to 1.0μ in diameter. Despite the fact that the psittacosis agent is closely related to viruses and has caused cardiac inflammation in both human infections and experimentally infected animals, until this writing it has not been considered in the etiology of myocarditis in infancy.

Report of Case

Chief Complaint.—Rapid respirations, one day.

Present Illness.—The patient was an 18-month-old girl who was admitted to the U. S. Army Hospital, Camp Zama, Japan, on Jan. 16, 1958, at 3 p. m. A week prior to admission the child was described as irritable unless carried about. There was no history of fever, but it was noted the child perspired easily. The patient had not eaten well

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for the previous few days before admission, refusing even milk on the day of admission. No cyanosis was noted.

Past History.—The infant was the product of a full-term normal pregnancy and delivery. She had four older siblings, all male, who were in very good health. The patient had always eaten well, and there was no history of dietary insufficiency. She had had the usual childhood immunizations without difficulty and had been completely well up to the present illness.

Physical Examination.—Physical examination revealed a well-developed well-nourished Caucasian girl, appearing pale and restless. The temperature was 101 F (rectally); heart rate, 160; respirations, 72 per minute, and weight, 23 lb. Ears, eyes, nose, and throat were normal. Fine moist rales were heard over both lungs. The heart was enlarged to the left. No murmurs were heard. The liver extended 4 fingerbreadths below the right costal margin, but the spleen was not felt. The genitalia were normal.

Laboratory Examination.—The white blood cell count was 11,000, with 46% neutrophils and 53% lymphocytes. The hemoglobin was 11.4 gm. per 100 ml. A urinalysis was not done. Chest x-ray revealed generalized cardiac enlargement and accentuation of the vascular markings consistent with congestive failure. An electrocardiogram revealed changes consistent with left ventricular hypertrophy (mean QRS vector pointing to the left and posteriorly with a deep S in Leads V_1, V_2, and V_3) and left atrial enlargement or pulmonary hypertension (tall and broad P waves in Leads L_2, L_3, and aV_F).

Course in the Hospital.—Digitalization was attempted at 7 p. m. on the day of admission with elixir of digoxin at a dosage of 0.04 mg. per pound. One cubic centimeter of mersalyl sodium and theophylline (Salyrgan-Theophylline) was given, and the infant was placed in oxygen. She, however, vomited the medication, and digitalization was attempted with lanatoside C (Cedilanid) at a dosage of 0.03 mg. per pound. The cardiac rate remained 160, and the rapid respirations persisted. At 9 p. m. a second dose of lanatoside C was given with 1.5 mg. of morphine. No change was noted. At 1:30 a. m., Jan. 17, 1958, the infant was given the last dose of lanatoside C calculated for full digitalization. She showed no improvement and died at 3:30 a. m., Jan. 17, 1958. The autopsy was done at the 406th Medical General Laboratory, at 9 a. m., Jan. 17, 1958.

On Feb. 6, 1958, two parakeets at the patient's home died. They were brought to the Veterinary Department of the 406th Medical General Laboratory, where a suspension of liver and spleen was prepared and passed intracerebrally, intranasally, and intraperitoneally into mice. A psittacosis agent was easily demonstrated from the moribund mice with use of Macchiavello's stain on smear preparations of brain and lung.[12] Further questioning of the parents revealed that the birds had been purchased in Yokohama, Japan, where presently no controls on psittacosis exist. It was also learned that the child had had numerous close contacts with both birds.

Autopsy Findings.—General: Examination revealed a well-developed well-nourished Caucasian girl with moderate cyanosis of the nail beds. Primary incision revealed the liver extending 6 cm. below the right costal margin, with a blunt rounded edge. The heart extended 10 cm. across the thorax, whose transverse diameter was 13 cm. Straw-colored fluid was present in the pleural cavities, whose membranes were smooth and glistening. A bilobed slightly atrophied thymus was identified in the mediastinum.

Lungs: The left lung weighed 140 gm.; the right, 135 gm. The pleural surfaces were smooth and glistening. There was markedly reduced crepitation. Cut surfaces revealed serosanguineous fluid which freely exuded.

Heart: The heart weighed 123 gm., and was markedly dilated. The valves, septa, and vessels were intact. The right and left ventricular walls were hypertrophied, measuring up to 0.7 and 1.5 cm. in thickness, respectively. Present on the mitral valves were translucent gray glistening elevations

Fig. 1.—Patient's chest x-ray, showing an enlarged dilated heart and increased vascular markings. The scattered patchy pneumonitis is not visualized.

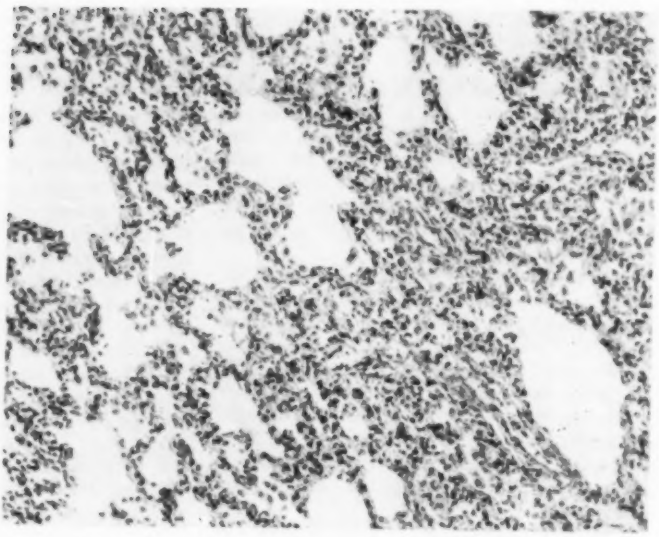

Fig. 2.—Lung of patient, showing patchy pneumonitis composed of macrophages and thickened septa. There is little relation to bronchi. Hematoxlin and eosin; reduced about 15% from mag. × 200.

measuring up to 0.2 cm. in diameter. The myocardium was firm but pale.

Liver: The liver weighed 200 gm. Cut surface revealed the usual lobular pattern, with accentuation of the central veins due to hyperemia.

Spleen: The spleen weighed 20 gm.

Other Organs: The remainder of the organs, including the brain, revealed no significant abnormalities.

Histopathology.—Methods: All tissues were fixed in 10% formalin. Tissue sections were stained with hematoxylin and eosin. Noble's modification of the Macchiavello method was used[12] and also Giemsa, Heidenhain's iron hematoxylin, Warthin-Starry, Gridley fungus, and Gram stains.[13] Lung sections of the mice infected with the psittacosis agent isolated from the patient's birds revealed a pneumonitis with characteristic inclusion bodies of psittacosis. Sections of the brains of the infected mice revealed meningitis, with inclusion bodies again easily seen. The morphology of the pneumonitis and inclusion bodies was exactly similar to that described by Weiss in his study of experimental psittacosis infections of mice.[14,15] Sections of mouse lung and brain showing the inclusions were used as controls for the staining procedures carried out on the human tissues.

Lung: Sections revealed acute hyperemia and edema. Present in scattered patchy areas not related to bronchi were groups of large macrophages present in the alveoli. In these areas moderate atelectasis and emphysema were seen, with clear spaces in the alveoli surrounded by edema fluid. There was hyperplasia of the lining alveolar cells manifested by cells along the surfaces of the septa with pleomorphic nuclei and abundant amphoteric cytoplasm. The bronchi were uninvolved by the process but were slightly dilated. The inflammatory response consisted predominately of macrophages, with a very occasional lymphocyte and neutrophil. The bronchial lymph nodes were enlarged, owing to edema and an infiltration of neutrophils and macrophages in the sinuses. Inclusion bodies were found in the cytoplasm of macrophage-type cells of the lungs. The nuclei of these cells were usually seen, but in some the condensation of the inclusions obscured its outline. The cells varied from a round, well-defined cell measuring up to 20μ in diameter to one having irregular strands of of cytoplasm containing inclusion bodies extending outward into the interstitial tissue. The cells were found in the alveolar spaces, in the septa, and in the stroma surrounding larger bronchi and pulmonary vessels. The inclusion bodies themselves were best observed by the Giemsa stain and Noble's modification of the Macchiavello stain. With these procedures they were basophilic with a violet hue. In form they were coccoid, with diameters of less than 1μ. Controls using the brain and lung of the infected mice showing inclusion bodies were used with each staining procedure. Comparisons were made between the mouse tissue and sections of the human material. The inclusion bodies corresponded exactly in form, color, and size.

Heart: Sections of myocardium revealed prominent interstitial foci of monocytes, macrophages, and lymphocytes. The muscle cells for the most part were separated by the infiltrate, but there was also necrosis of muscle fibers. Foci of inflammatory cells were also seen in the pericardium. Sections of the mitral valve revealed scattered lymphocytes and monocytes below the endocardium.

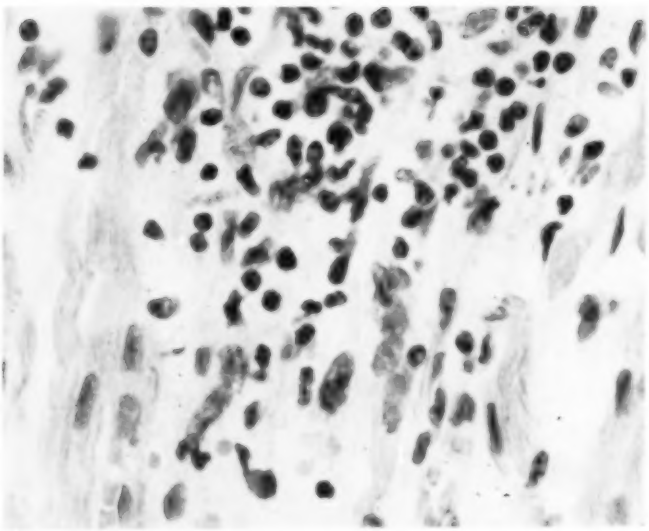

Fig. 3. — Myocarditis composed of macrophages and lymphocytes with necrosis and separation of muscle fibers. Hematoxylin and eosin; reduced about 15% from mag. × 600.

Immediately below the endocardium of the papillary muscle of the anterior leaf of the mitral valve was a very prominent infiltrate of lymphocytes and macrophages along with a slight proliferation of endothelial cells over this area. Large macrophage-cells containing the above-described inclusion bodies were easily seen in the interstitial areas of the myocardium.

Liver: Sections of liver revealed a mild fatty metamorphosis. There was an increase of lymphocytes and monocytes in the periportal areas. Macrophages containing the above-described inclusion bodies were present in the periportal areas. Inclusion bodies were also seen in an occasional Küpffer cell.

Spleen: Sections revealed a prominence of follicles which had well-developed germinal centers surrounded by lymphocytes. There was a marked hyperemia of the sinuses. Macrophage cells with the above-described inclusions were seen but only with great difficulty.

Other Organs: Other organs, including the brain, revealed no significant abnormalities.

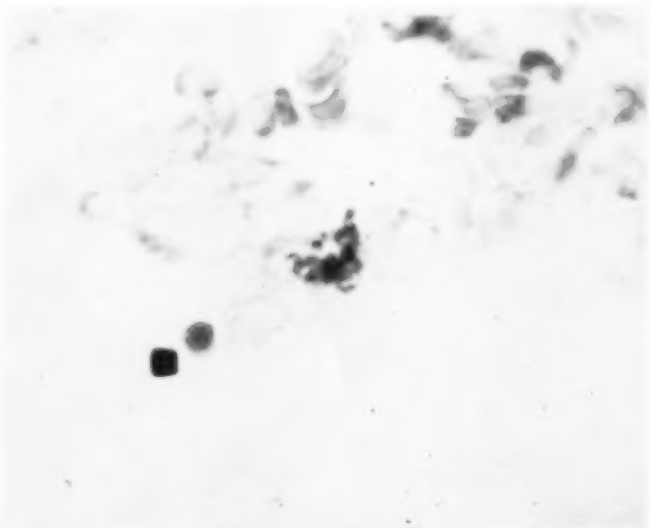

Fig. 4.—Psittacosis inclusion bodies in a large macrophage of mouse lung infected with the strain of psittacosis isolated from the patient's parakeets. Used as a control for staining procedures carried out on the patient's tissues. Giemsa stain; reduced about 15% from mag. × 3000.

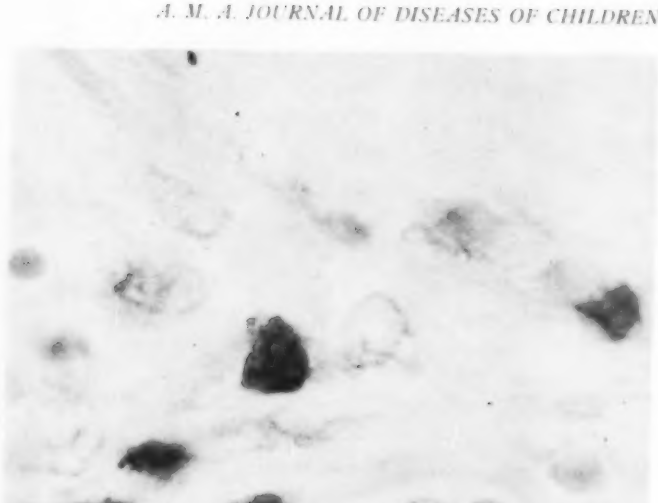

Fig. 5.—Intracytoplasmic inclusions present in a macrophage cell of patient's lung. Giemsa stain; reduced about 15% from mag. × 3000.

Diagnoses.—The immediate cause of death was congestive heart failure due to myocarditis. The basic cause of death was pneumonitis and myocarditis due to a psittacosis agent.

Comment

The clinical course of sudden heart failure with cardiac enlargement and nonspecific electrocardiographic changes in a child under 2 years of age fits exactly the clinical description of myocarditis in infancy. Gross and microscopic findings of an enlarged dilated heart, congested lungs, and myocarditis compare exactly to Saphir's autopsy descriptions of the process.[2] When one considers a specific etiology for the myocarditis, the clinical history of close association with two parakeets who later died of psittacosis strongly suggests a relationship. The finding of pneumonitis manifested by alveolar-cell hyperplasia, a response of macrophages,

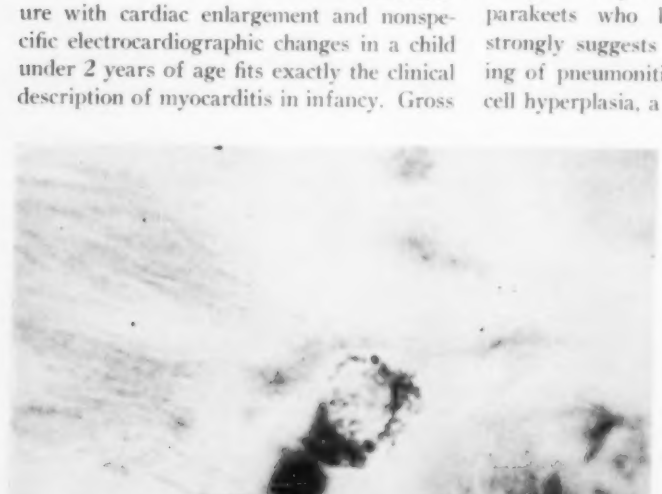

Fig. 6.—Intracytoplasmic inclusions in a macrophage cell of patient's myocardium. Individual inclusions are easily seen. Giemsa stain; reduced about 15% from mag. × 3000.

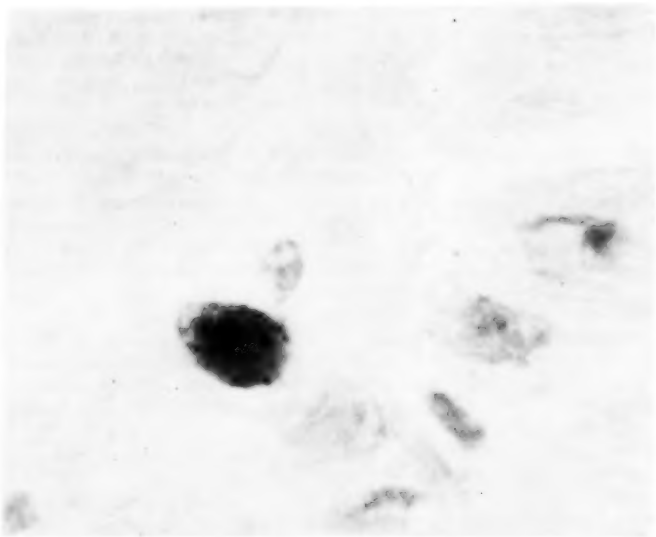

Fig. 7.—Inclusions in patient's myocardium. Noble's modification of the Macchiavello's method; reduced about 15% from mag. × 3000.

and little infiltration of the septa, with no involvement of the bronchi, provides the characteristic morphology of psittacosis pneumonitis and strongly indicates the presence of a psittacosis agent. The finding of characteristic inclusion bodies in the heart, lungs, and liver of the patient, which were exactly similar to those obtained from the patient's birds, provides a firm basis for identification of the organism. The fact that psittacosis has produced cardiac hypertrophy and myocarditis in human material gives further support to the diagnosis. It is also interesting that Levinthal, who gave his name to the inclusion bodies, described them in the pericardial fluid of experimental animals.

Cardiac involvement in psittacosis has in recent literature been almost completely overlooked. The purpose of this paper is

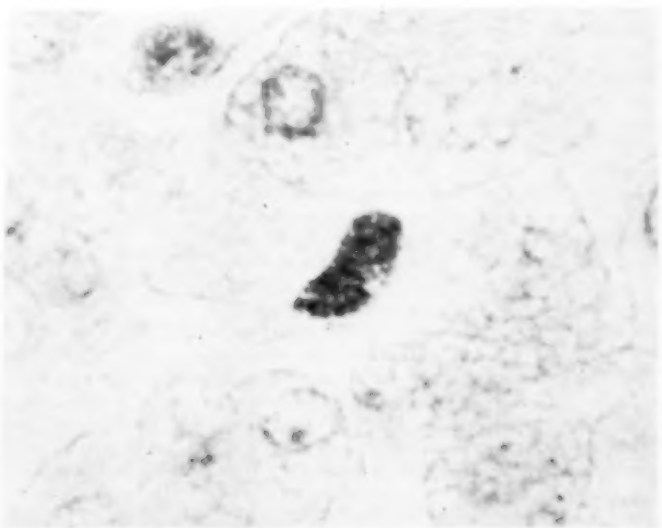

Fig. 8.—A Küpffer cell filled with intracytoplasmic inclusion bodies. Giemsa stain; reduced about 15% from mag. × 3000.

to call attention to the relationship that occurred between psittacosis and myocarditis in this patient in order to stimulate interest in searching for any possible relation between this group of organisms and future cases of myocarditis.

Summary

A case in an 18-month-old child of myocarditis due to a psittacosis agent is recorded, with autopsy findings.

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Pyoderma Gangrenosum

Pseudomonas Infection Versus the Shwartzman Phenomenon

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Acute necrosis of the skin occurs rarely in infants. Previous reports concerning this condition have emphasized bacterial infection as a primary cause. Very little attention has been given to the Shwartzman phenomenon as an etiologic factor. Our interest in this problem was stimulated by an infant we recently cared for at the Children's Memorial Hospital.

Report of Case

A 7-week-old American Indian girl was admitted to the hospital on Sept. 3, 1957, because of purulent drainage from both ears and a rash. She had been sick for eight days with a fever and cough. The cough had subsided before admission. Five days after the onset of the illness she developed a rash which involved only the face and then spread over the trunk and extremities. She received no medication before hospitalization.

She was the product of a normal pregnancy and delivery. Her birth weight was 7 lb. 6 oz. Her diet prior to the onset of her illness was a simple evaporated milk formula.

Physical examination on admission revealed a well-developed well-nourished infant who was somewhat irritable but in no acute distress. Temperature was 104.4 F rectally. Weight was 10 lb. There was a maculopapular rash on the face and extremities and a papulopustular rash on the chest and back. The pustular lesions were most pronounced on the back and buttocks. A purulent cheesy exudate was present in both ear canals and blocked the view of the eardrums. There was a mucopurulent discharge from her nose. The pharynx appeared moderately injected. There was no cervical or other adenopathy. The lungs were clear to auscultation, and, except for a moderate tachycardia, the heart sounds were normal. Examination of the abdomen revealed the liver edge palpable 1 fingerbreadth below the right costal margin.

The admission diagnosis was bilateral suppurative otitis media and pyoderma. She was treated initially with intramuscular injections of penicillin and oral novobiocin.

Admission laboratory studies revealed the following findings: red blood cell count, 3,230,000; hemoglobin 8.5 gm.; white blood cell count, 18,100; differential count, neutrophils 15%, lymphocytes 56%, and monocytes 29%; urinalysis, no abnormal findings; Kahn test for syphilis was negative. Total serum proteins were 5.7 gm. (albumin 3.2 gm., globulin 2.5 gm., and γ-globulin 1.2 gm.). Culture of the ear discharge revealed Staphylococcus pyogenes var. aureus. Throat culture revealed Diplococcus pneumoniae, Streptococcus mitis, Escherichia coli, and a few nonhemolytic staphylococci. An organism of the paracolon group was cultured from the blood.

She became afebrile in 36 hours. Two days after admission the rash on her face, neck, and chest had cleared, with only fine scaling and a few faint macules remaining. No new skin lesions had formed. The ears had stopped draining. She was very active and took feedings well. A repeat of the blood culture at this time showed no growth.

On the third hospital day the lesions on the back and buttocks were observed to be getting larger. Several areas had developed circumscribed ecchymotic centers, and new lesions were appearing on the back. She regurgitated a few times and appeared more toxic than on previous days. Culture of material taken from her back showed Pseudomonas aeruginosa to be present. Before the culture result was known, the penicillin and novobiocin were discontinued, and chloramphenicol intramuscularly was started. The infant was kept on her abdomen, and the back and buttocks were left uncovered. Topical therapy was not used. The progress of the eruption was halted, and new lesions ceased to appear.

On the fourth day her white blood cell count was 28,200 and the differential count was as follows: neutrophils, 58% with 12% band forms; eosinophils 4%, lymphocytes 20%, and monocytes 18%.

After the first hospital week the back and buttocks eruption appeared to be healing. Almost all the lesions had sharply demarcated necrotic plug-

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Departments of Pediatrics, Children's Memorial Hospital, Otho S. A. Sprague Memorial Laboratories, and Northwestern University Medical School (Dr. Kohlenbrener and Dr. Boehm); Departments of Dermatology, Children's Memorial Hospital and the University of Illinois College of Medicine (Dr. Falk).

Fig. 1.—Pyoderma gangrenosum, showing discrete patches of necrosis.

Fig. 2.—Healing pyoderma gangrenosum, showing scarring.

like centers and rolled edges (Fig. 1). A culture was taken of material from under one of the eschars, and again Pseudomonas was revealed. Disc sensitivity studies done on the original Pseudomonas culture had shown the organism to be moderately sensitive to sulfadiazine and the tetracycline drugs and insensitive to polymyxin and chloramphenicol. However, because of the apparent response to chloramphenicol the drug was continued orally. Sulfadiazine was added to the regimen.

After the second hospital week almost all of the eschars had sloughed, leaving ulcers with clean granulating bases. The white blood cell count was then 10,300, with a normal differential count.

After three weeks the ulcers were all decreasing in size. She had gained 1 lb. over the admission weight. Chloramphenicol and sulfadiazine were discontinued. Improvement continued, and after the fourth week many of the smaller lesions had healed completely, with little scarring. The largest lesion on the right buttock was covered with a dark thick crust. However, it had shrunk to about one-half its maximum size (Fig. 2).

On leaving the hospital, five weeks after admission, the patient had gained 1¾ lb. and only a few crusts remained.

Comment

P. aeruginosa was cultured twice from the necrotic skin lesions on this infant. It was presumed that this organism was the cause of the lesions, and the antibacterial therapy was directed against it. She responded well, and it is attractive to assume that her response proves that the working assumption of the etiology was correct. Description in the literature of skin lesions due to Pseudomonas also support this assumption. However, there are features of this case that are unusual, and the evidence for Pseudomonas may be circumstantial and misleading.

The skin lesion due to Pseudomonas infection has been described as characteristic.[1] As in this case, an innocuous-appearing rash rapidly progresses through ecchymosis to necrosis and ulceration. The necrotic areas are sharply demarcated, and there is minimal inflammatory reaction around the lesions. The ulcers have rolled edges which are not undermined.

Previous cases in which children with Pseudomonas skin infections have been reported stressed predisposing factors that rendered the patient more susceptible to infection by this organism. Intensive antibiotic therapy for a prior severe infection permits

the antibiotic-resistant Pseudomonas to overwhelm the exhausted mechanisms of natural defense.[2] Most of the reported cases with skin manifestations had bacteremia and generalized sepsis as well. Premature infants are more prone to infection with this organism than older infants. One report emphasizes that treatment of premature and possibly full-term infants with high-humidity environment predisposes the infant to Pseudomonas skin infections.[3]

The case presented here is not typical of those that have been described with Pseudomonas skin infections. The patient was a normal 6-week-old infant when the acute illness began. The illness evolved without medication into a bilateral otitis media which did not cause serious debility but which was unusual in that a rash was present. Penicillin and novobiocin therapy caused rapid remission of the otitis. Much of the rash subsided also, but the severer pustular lesions on her back and buttocks progressed to necrosis and ulceration.

The Shwartzman phenomenon can produce necrotic skin lesions that are identical with the ones found in this case. This phenomenon of altered tissue reactivity has been given very little attention by pediatricians. Dermatologists and allergists are more cognizant of it, and many believe that it is an important etiologic factor in pyoderma gangrenosum. Rostenberg[4] reviewed the literature concerning this phenomenon and its possible skin manifestations.

A brief explanation of the experimental Shwartzman phenomenon might be helpful. The tissue to be sensitized is prepared by injection (interstitially or into its vascular supply) of a filtrate of bacterial products. An interval of 12 to 24 hours must separate the preparatory injection from the eliciting injection. The eliciting material may be the same as the preparatory material, or it may be entirely different. A new and unrelated bacterial filtrate, substances such as kaolin and agar, or the products of an immunologic reaction may be used to elicit the phenomenon. The eliciting material must be injected intravenously. There is no significant antibody production during the interval. The phenomenon is dependent on transiently altered tissue reactivity and not on an antigen-antibody reaction. In this way it differs from the Arthus phenomenon, which can also produce identical necrotic lesions.

The skin lesions of the experimental Shwartzman phenomenon appear about four hours after the eliciting injection. The sequence is from localized hemorrhage to necrosis. The reaction can be generalized and fatal if the preparatory dose is given intravenously.

It is probable that the Shwartzman phenomenon occurs naturally, and many clinical conditions, including ulcerative colitis and pyoderma gangrenosum, have been theoretically explained by it.[4] There is no way of proving that the necrotic skin lesions of our case were a manifestation of the Shwartzman phenomenon. On the other hand, there is no way to prove that they were not.

Summary

The case of a 2-month-old infant who had necrotic progression of a rash associated with otitis media is described. Pseudomonas was cultured from the skin lesions, and antibiotic therapy seemed to be successful. The etiologic role of Pseudomonas was not proved, and features of the case are unusual. The possible importance of the Shwartzman phenomenon is discussed.

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Renal-Cell Adenocarcinoma in Children

Report of a Case

RAÚL A. MARCIAL-ROJAS, M.D.; BENIGNO RODRÍGUEZ-LUCCA, M.D., and RICARDO ALONSO, M.D.,
San Juan, P. R.

Fig. 1.—Ascending pyelogram, showing marked hydronephrosis and marked irregularity of the upper ureter.

Kidney tumors in children are almost always embryonal nephroblastomas, commonly known as Wilms' tumors. These are only second in frequency to neuroblastomas among malignant neoplasms in children. The occurrence of renal-cell adenocarcinoma, usually termed hypernephroma, is most unusual in children.

In 1938 Ladd [1] stated that he had not seen a single example of hypernephroma in 20 years at the Children's Hospital. He also commented that from a study of the literature the occurrence of true hypernephroma in childhood appears to be very rare.

Bell [2] stated that about 95% of renal adenocarcinomas develop in persons over 40 years of age and doubted very much their existence in childhood. Melicow [3] could not find a single instance of renal adenocarcinoma in children among his review of 199 cases of renal tumors.

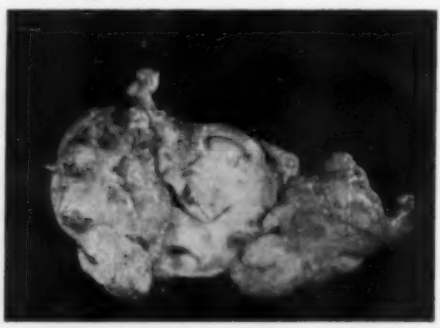
Campbell [4] could only find four such tumors in the files of The American Tumor Registry. Cathcart [5] reported one case in a 14-year-old boy from Mayo Clinic in 1929. This case is included among the four mentioned by Campbell and was again reported with an additional case by Hempstead.[6]

Johnson and Marshall [7] found 2 cases of renal-cell carcinoma and 3 of papillary adenocarcinoma among 64 cases of renal tumors in children seen over a period of 25 years. The rest were Wilms' tumors.

Carlson [8] added another case and presented a careful review of the literature which disclosed 24 cases of this type of tumor in children. He mentioned his knowledge of two additional cases by personal communication.

Hogan [9] recently reported an additional case encountered during an exploration for correction of an ureteral anomaly. We have lately seen another case in an 8-year-old girl, which is the subject of the present communication.

Fig. 2.—Bisected kidney with half of the pedunculated tumor reflected laterally. The renal pelvis is markedly dilated.



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From the Department of Pathology of the University of Puerto Rico School of Dentistry and the I. González-Martínez Oncologic Hospital; Consultant Pathologist to the Department of Health District Hospitals (Dr. Marcial-Rojas); from the Department of Urology of the University of Puerto Rico School of Medicine and the Fajardo District Hospital (Dr. Rodríguez-Lucca); from the Department of Pediatrics of the Fajardo District Hospital (Dr. Alonso).

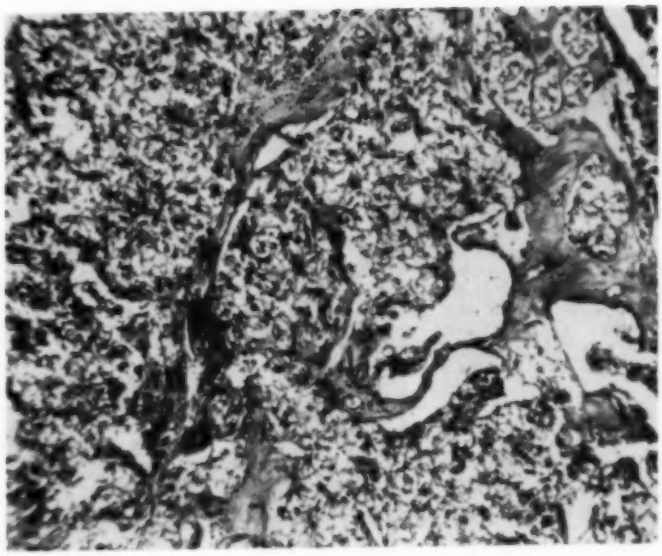

Fig. 3.—Areas of classical clear-cell adenocarcinoma of kidney. Hematoxylin and eosin; reduced 20% from mag. × 100.

Report of Case

An 8-year-old girl was admitted to the Fajardo District Hospital in November, 1956, because of silent gross hematuria of several days' duration. She had had episodes of hematuria for the previous three years. These lasted around 7 to 10 days and were sometimes accompanied by frequency and burning on urination. She was previously treated by her physician for a presumptive diagnosis of acute glomerulonephritis.

The systemic review of symptoms was noncontributory, and so was the physical examination. The urine revealed persistent albuminuria and microscopic hematuria. Casts were not seen. Urine culture was sterile after 48 hours. Blood chemistry was within normal limits. The blood studies disclosed moderate hypochromic anemia.

The intravenous urogram demonstrated a normal left upper urinary tract but failed to visualize the right kidney. Radiography of the chest was negative.

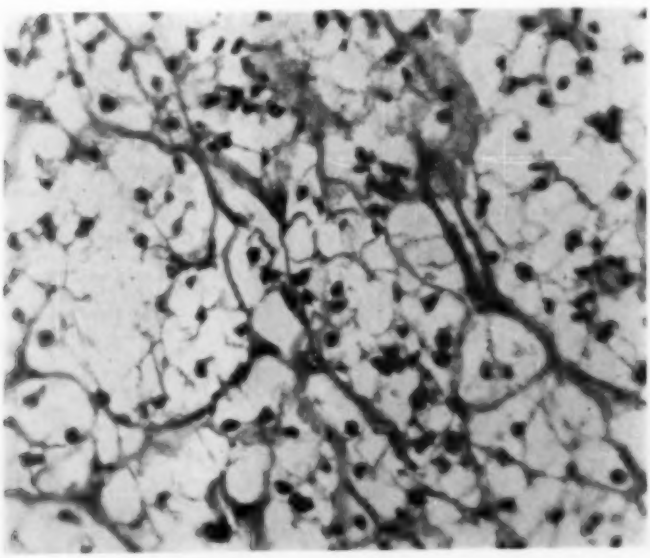

Fig. 4.—Areas similar to those shown in Figure 3. Hematoxylin and eosin; reduced 20% from mag. × 360.

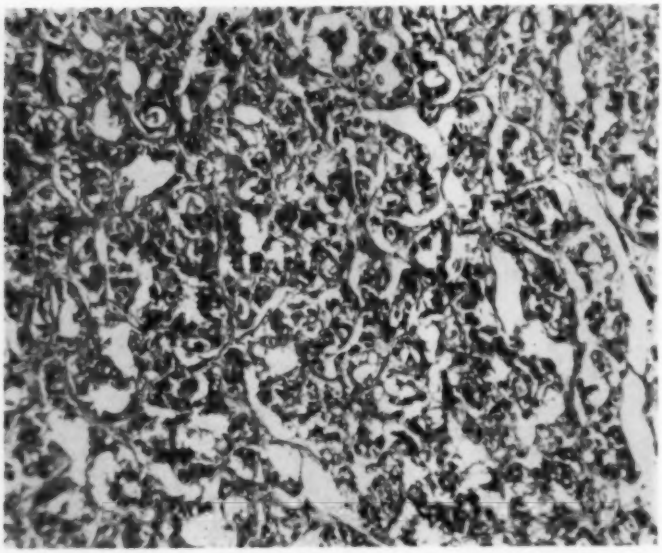

Fig. 5.—Zones of the tumor showing the granular-cell component of renal-cell carcinoma. Hematoxylin and eosin; reduced 20% from mag. × 100.

On cystoscopic examination no abnormalities were encountered in the bladder. The right ureteral orifice was easily catheterized, and an ascending pyelogram was performed. It exhibited marked hydronephrosis with irregularities in the upper ureter (Fig. 1).

The tuberculin test was positive. Despite negative acid-fast stains of the urinary sediment the patient was given streptomycin, aminosalycylic acid, and isoniazid for three weeks prior to surgery. The preoperative diagnosis was tuberculosis of the right kidney and ureter. On Jan. 21, 1957, under general anesthesia, a right nephroureterectomy was performed. The patient had an uneventful postoperative course and was discharged on the 12th postoperative day. Urine culture for tubercule bacilli did not show growth after six weeks of incubation. The last time that the patient was seen, on May 20, 1958, she was completely free of disease. The radiographs of chest and bones were negative.

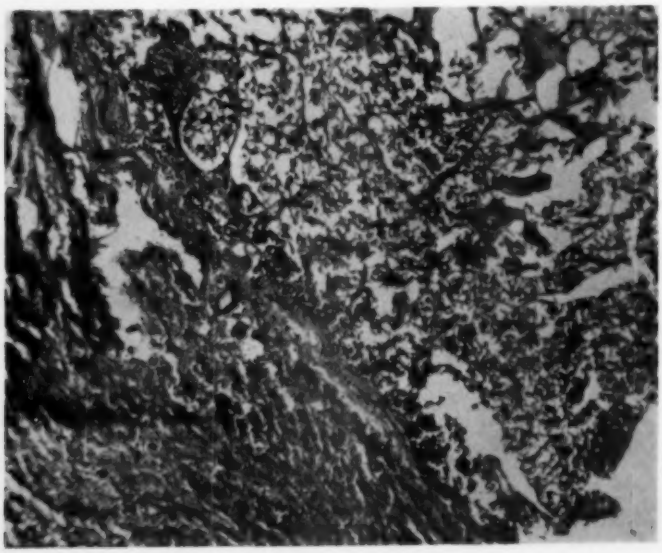

Fig. 6.—The relation of the tumor to the renal pelvis is very well demonstrated here. Hematoxylin and eosin; reduced 20% from mag. × 100.

Pathologic Findings.—Gross Description: The kidney measured 7×4×2 cm. The capsule stripped off easily. The surface still showed prominent fetal lobulations. The renal pelvis was markedly dilated and occupied by a lobulated tumor measuring 6×4 cm. which extended into the dilated calices. The tumor was free over most of its surface but continuous with the compressed and atrophic renal parenchyma at a broad pedicle, 3.5 cm. in length. On section it was yellowish-orange and soft and had small areas of hemorrhage (Fig. 2).

Microscopic Description: The tumor was composed of areas of neoplastic but fairly well differentiated renal tubules (Fig. 3) alternating with others of more solid tumor formed by sheets and cords of polygonal clear cells (Fig. 4). The vascularity of the tumor was prominent.

Comment

Silent gross hematuria in children is usually the result of medical renal disease. This case illustrates the importance of complete urological work-up in children complaining of gross hematuria.

Renal-cell carcinoma, although very rare in children, should always be kept in mind in the differential diagnosis of painless gross hematuria. Wilms' tumor is by far the most frequent renal neoplasm encountered in children, but it is usually manifested by the presence of a rapidly growing palpable intra-abdominal mass and only occasionally accompanied by gross hematuria. Silent gross hematuria is seldom the unique symptom in embryonal tumors of the kidney.

The preoperative diagnosis in this case could not be definitely established because the pyelographic findings were those of hydronephrosis and hydroureter of no apparent cause. This was due to the fact that the tumor was growing as a polypoid mass into the renal pelvis, producing hydronephrosis and not giving the typical radiographic findings of an intraparenchymatous neoplasm.

Although renal tuberculosis in childhood is rare, it was considered in the preoperative diagnosis because of the destruction of renal parenchyma, a positive tuberculin test, and the absence of apparent obstruction.

Summary

A case of renal-cell adenocarcinoma in an 8-year-old girl is presented. The tumor was growing as a polypoid mass into the renal pelvis, producing marked hydronephrosis and gross silent hematuria. We believe this represents the 28th reported instance of this type of tumor in children. The importance of complete urologic investigation in children complaining of gross silent hematuria to rule out the possibility of renal-cell carcinoma is emphasized.

Department of Pathology, School of Tropical Medicine.

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Abstracts from Current Literature

New England Journal of Medicine, Boston

Abstracted by Demetrius G. Traggis, M.D.

258, No. 11 (March 13) 1958

* The Febrile Convulsion in Shigellosis. M. Kowlessar and G. B. Forbes.—p. 520.
Bacterial Variations in the Nasopharynx and Skin of Isolated Arctis Scientists. R. W. Christie.—p. 531.
Current Concepts in Therapy.—p. 544.

The Febrile Convulsion in Shigellosis.—The authors made a statistical analysis of 246 cases of shigellosis with regard to the presence or absence of convulsions in order to try and determine the etiology of the convulsions which are frequent in children.

In their cases no patient suffered more than one convulsion. Eight patients died, two of whom had had a convulsion. Lumbar puncture was negative in all 38 cases in which it was done. Of the 246 patients (age range from a few months and including adults) 29 patients (12%) had a convulsion. No convulsion was seen in age groups over 7 years. The highest number was at the age of 3 years. Forty-two per cent of the children whose temperatures were over 104 F had a convulsion (none of 23 children and adults with temperature over 104 F had a convulsion). The authors also confirmed the observations of others that children with history of previous convulsions or family history of convulsion are more likely to convulse. This, again, was a function of age. No other factors, such as concurrent disease or associated nervous system symptoms, could be incriminated. Likewise, sex did not seem to be a factor. There was no evidence to decide whether or not a neurotoxin is involved.

Pediatrics, Springfield, Ill.

Abstracted by William W. Cleveland, M.D.

20, No. 6 (Dec.) 1957

Phagocytosis in Premature Infants. Louis Gluck and William A. Silverman.—p. 951.
Immunologic Studies in Congenital Agammaglobulinemia with Emphasis on Delayed Hypersensitivity. Herbert M. Porter.—p. 958.
Progressive Hereditary Diaphyseal Dysplasia. Kenneth F. Stegman and J. C. Peterson.—p. 966.
Two Additional Examples of Viremia in Asymptomatic Poliomyelitis Infection. David C. Davis and Joseph L. Melnick.—p. 975.
Evaluation of the Skeletal-Age Method of Estimating Children's Development: III. Comparison of Measurement and Inspection in the Assessment of Roentgenograms. Donald Mainland.—p. 979.
* Sterilization and Preservation of Formulas for Infants. Henry K. Silver.—p. 993.
Cat Scratch Disease as a Cause of the Oculoglandular Syndrome of Parinaud. Andrew M. Margileth.—p. 1000.
Unilateral True Hermaphroditism: Two Cases with Sex-Chromatin Positive Cellular Pattern. Ira M. Rosenthal, Joseph H. Kiefer, Elizabeth McCrew, and I. Pat Bronstein.—p. 1006.
Accidental Infection with Vaccinia Virus: A Case Report Illustrating Laboratory Studies and Problems of Vaccination. Henry G. Cramblett, Clarence F. Szwed, John P. Utz, Julius A. Kasel, and Norman B. McCullough.—p. 1020.
Indications for Excretory Urography in Children. John Askin, Thomas Reichelderfer, Julian Salik, and Jules Merritt.—p. 1033.
Social Change and Child Health: The Fourth Kenneth D. Blackfan Memorial Lecture. Richard W. B. Ellis.—p. 1041.
Gesel Tests on African Children. Marcelle Geber and R. F. A. Dean.—p. 1055.
Newly Isolated Viruses in Respiratory Disease. Robert H. Parrott.—p. 1066.
Pediatric Group Practice. Arthur J. Moss, Neil N. Litman, Wilbert Liebling, Sheldon C. Siegel, and Bailey J. Lovin Jr.—p. 1084.
Professional Education and Mental Retardation. Grover F. Powers.—p. 1088.
Annual Summary of Vital Statistics—1956. Myron E. Wegman.—p. 1095.
Hypoparathyroidism in Children and Adolescents. Robert T. Soper, Edward E. Mason, and Joseph A. Buckwalter.—p. 1097.
Infections Due to Adenoviruses. Heinz F. Eichenwald.—p. 1108.

21, No. 1 (Jan.) 1958

* Response of the Young Infant to Poliomyelitis Vaccine Given Separately and Combined with Other Antigens. Randolph Batson, Amos Christie, Bertha Mazur, and Jewell H. Barrick.—p. 1.
The Presence of Serratia Marcescens as the Predominating Organism in the Intestinal Tract of the Newborn: The Occurrence of the "Red Diaper Syndrome." Harry A. Waisman and William H. Stone.—p. 8.
Determination of Some Streptococcal Antibody Titers and Acute Phase Reactants in Patients with Chorea. T. N. Harris, Sidney Friedman, and David C. McLean.—p. 13.

Ammonia in the Blood in Newborn Infants. Raymond L. Clemmens, Shelia B. Shear, and Samuel P. Bessman. —p. 22.
Hematologic Studies of Children with Lead Poisoning. R. Janet Watson, Elisabeth Decker, and Herbert C. Lichtman.—p. 40.
Concerning the Choice of Therapy for Childhood Hyperthyroidism. Mary B. Arnold, Nathan B. Talbot, and Oliver Cope.—p. 47.
Benign Familial Polycythemia in Childhood: Report of Two Cases. Marvin L. Auerback, James A. Wolff, and Stacy R. Mettier.—p. 54.
Hypertension and Hypercalcemic Nephropathy Due to Vitamin D Intoxication: A Case Report. William G. Way, David L. Morgan, and Lee E. Sutton Jr.—p. 59.
A Comparison of the Effects of Whole Blood and Sedimentated Erythrocytes in Exchange Transfusion. Thomas R. C. Sisson, Lorraine E. Whalen, and Amalia Telek.—p. 81.
Acute Idiopathic Hydrops of the Gallbladder Not Due to Calculi, Possibly to Infectious Hepatitis: Report of Two Cases in Neighboring Children. John J. McGahan and John A. Whittinghill.—p. 91.

Sterilization and Preservation of Formulas for Infants.—Common techniques for formula preparation as practiced in the home were assessed as regards their efficiency in sterilization of formula. The usual nonpressure terminal heating method of preparation was used, and various conditions of subsequent storage as regards temperature were evaluated by periodic cultures of the milk. The growth of several pathogenic micro-organisms added to bottles of formula prior to terminal heating was also tested. In uninoculated formula prepared according to this technique and stored at 4.4 C immediately after heating, there was no growth of organisms even for periods up to seven days; when bottles were stored at 21 to 24 C or at 37 C, however, nonpathogenic air-borne Bacillus subtilis was cultured from most of the bottles. No growth of added pathogenic organisms was noted following terminal heating, regardless of subsequent storage temperature, although, again, bottle stored at room temperature revealed a heavy growth of B. subtilis. It was also found that when bottles containing milk scum from previous experiments were used some of the formula units contained a heavy growth of B. subtilis, regardless of experimental conditions used. From these results the author concludes that terminal heating of formula is a very safe means of preparing formula and that formula so prepared, immediately cooled, and refrigerated is bacteriologically safe for periods of two to three days and that a new supply of formula need not be prepared each day. It is further pointed out that keeping formula for six hours or more at room temperature following heating may lead to gross contamination by bacteria dormant in the milk and also that inadequate cleaning of bottles prior to use greatly enhances the danger of contamination.

Response of the Young Infant to Poliomyelitis Vaccine Given Separately and Combined with Other Antigens.—In this study two groups of 50 infants each were immunized according to the following schedule: at 6 weeks, 12 weeks, and 10 months of age 1 ml. of poliomyelitis vaccine was given; pertussis and smallpox vaccines were given at 6 weeks, and diphtheria-pertussis-tetanus was given at 3, 4½, and 6 months. In Group I the poliomyelitis vaccine and other antigens were given on the same visit but at different sites, while in Group II the poliomyelitis vaccine was given in the same syringe with the other vaccine. Blood was drawn at the time of each injection and also two weeks and four or more months after the third, or booster, injection; the specimens were analyzed for antibody response to the various antigens. Although not all of the infants had completed the study, sufficient data were collected to indicate that a satisfactory response to this program of immunization was observed and that no difference was noted when the vaccines were given as separate injections or when combined prior to injection. The incidence of adverse reactions was not increased over that usually encountered with the addition of poliomyelitis vaccine. The results are interpreted to indicate that poliomyelitis vaccination can be introduced early and in combination with other antigens to give satisfactory protection of the young infant.

Comment.—The results of this study contribute greatly to realizing more optimal immunization schedules. The need for data justifying a shorter interval between second and third poliomyelitis vaccine injections along with other ramifications of this paper is pointed up in the discussion of this work as presented at the 1957 meeting of the American Pediatric Society (A. M. A. J. Dis. Child. 94:404 [Oct.] 1957).

Radiology, Syracuse, N. Y.

Abstracted by William E. Anspach, M.D.

70, No. 2 (Feb.) 1958

* Idiopathic Pulmonary Hemorrhage with Hemosiderosis and Microcytic Anemia. Ernest L. Schoeniger, Arthur S. Tucker, and Robert P. Bolands.—p. 191.
* Chest Film Findinga in Neonatal Respiratory Distress. Gunter Schultze.—p. 230.

70, No. 3 (March) 1958

* Use of Air as a Contrast Medium in the Diagnosis of Intestinal Obstruction on the Newborn. John W. Hope and Edward O'Hara.—p. 349.

70, No. 4 (April) 1958

* Ascaris Ileus in Children. James J. McCort.—p. 528.
Premature Obliteration of the Sternal Sutures and Pigeon-Breast Deformity. Guido Currarino and Frederic N. Silverman.—p. 532.
Congenital Enteric Duplication Cyst: Report of a Case Diagnosed Roentgenologically. Bernard Kleppel.—p. 570.

Idiopathic Pulmonary Hemorrhage with Hemosiderosis and Microcytic Anemia.—Idiopathic pulmonary hemosiderosis was observed over a period of three years in a girl, starting at the age of 9. Expectoration of small amounts of blood-streaked sputum was the reason for admission to the Hospital. She was pale but not acutely ill. For several months she had had a low-grade fever with frequent respiratory infections. The physical examination was normal.

A regular chest roentgenogram showed streaky, mottled fine densities, which had a tendency to coalesce, diffusely distributed throughout the lungs. During a week's stay in the hospital the course was mildly febrile (maximum temperature 38 C) and slight hemoptysis continued. A chest roentgenogram 19 days later revealed a marked degree of improvement. Another episode of hemoptysis and fever occurred 10 weeks later, followed by rapid clearing. For nearly three years she remained relatively asymptomatic. Then she was admitted again to the hospital because of a bout of hemoptysis and fever of three days' duration. The appearance was that of a moderately acutely ill child. The nail beds appeared slightly cyanotic, and several rales and rhonchi were heard throughout the lungs. The chest film showed marked bilateral pulmonary infiltrations of the same nature as that found originally but were more extensive. On the fourth day the fever subsided and the chest film became normal. The patient was allowed to return home, only to be readmitted four months later after a sudden onset of bleeding which became progressively worse. The patient died of shock within an hour.

At necropsy the pleural surfaces of the lungs were glistening and presented a reddish-brown appearance, mottled with dark reddish-blue subpleural hemorrhages. Both lungs contained numerous dark red foci due to recent hemorrhage.

Microscopic examination showed markedly thickened alveolar walls, and hemosiderin was present in large amounts in the alveoli and their walls, either in the form of free granules or within macrophages.

The symptomatology in this disease has been strikingly similar in all recorded cases. The patients progress to tachypnea, dyspnea, pallor, tachycardia, low fever, slight cyanosis, and ultimate jaundice. Iron-deficiency anemia is striking, as the disease progresses. Clubbing of the fingers may be followed by cor pulmonale and heart failure.

The diagnosis should be considered in all young patients with hemoptysis who present a diffusely pulmonary infiltrate which changes, clears, and recurs.

Roentgenographically the appearance is usually characteristic.

Comment.—A case similar to this was observed and reported by me in 1939. At that time no published chest roentgenogram portraying this disease could be found in the literature.

Chest Film Findings in Neonatal Respiratory Distress.—An attempt is made to show a correlation of roentgenographic patterns with different pulmonary disease processes. Given pertinent clinical information, the etiology of these changes can often be suggested with confidence.

Chest roentgenograms in 100 infants, less than one month old, revealed that 20 had bilateral, coarse, diffuse, irregular densities (seven deaths). Twenty had reticulogranular densities (eight deaths). Miscellaneous patterns were found in 13 others, which included lobar infiltrations, pneumothorax, rounded radiolucent lesions, and changes suggesting massive atelectasis. Forty-seven were normal.

Of the 20 showing reticulogranular shadows, 18 were premature. There was no meconium-stained ammiotic fluid or fetal distress before birth. Ten had respiratory distress immediately after birth. Nine had clinically normal respirations from 1 to 36 hours postnatally.

The essential pathologic findings in one-third of the infants showing reticulogranular pattern was diffuse hyaline membrane disease with secondary atelectasis in a varying degree.

The clinical data for the surviving infants, except in one case (probable pulmonary infection contracted in utero) were entirely compatable with hyaline membrane disease. A well-known association with prematurity and/or limitation of the disease to the first 5 or 6 days of life was observed in all cases.

The author believes that disseminated neonatal atelectasis is secondary to obstruction of air rather than to primary failure of expansion. The reticulogranular pattern should therefore not be considered physiologic, in spite of the fact that the lungs in 60% to 80% cleared spontaneously.

Severe dyspnea resulting in cyanosis and convulsions as exhibited by several infants is not physiologic; likewise, sustained tachypnea is to be regarded with suspicion. Yet, original and follow-up chest films in these infants were normal and a subsequent course was benign.

The larger majority of infants that show a reticulogranular pattern during the first six days of life probably have hyaline membrane disease and not physiologic disseminated neonatal atelectasis. There is a tendency to overread neonatal chest films, especially when there is a convincing history of respiratory disease.

Use of Air as a Contrast Medium in the Diagnosis of Intestinal Obstruction of the Newborn.—The authors recommend the use of air instead of opaque media in making examinations of the intestinal tract in the newborn. Air is not only better because most obstructions have a high location but the child will receive less radiation during the examination.

Eight cases are used to illustrate how an obstruction can often be located by use of air contrast. When the stomach is found filled with fluid, the fluid is withdrawn and replaced with a similar quantity of air. Then the patient is tipped into different positions and the entire outline of the gas-filled chambers can be observed on roentgenograms. The relatively small quantity of irradiation caused by taking films compared with a much larger amount of radiation delivered by fluoroscopy only is an important point. Often fluoroscopy may not be necessary. The use of opaque contrast media in newborn infants seldom achieves a diagnosis.

In this connection, several of the recommendations published in the National Academy of Sciences National Research Council report are of interest. "(1.) The medical use of x-ray should be reduced as much as is consistent with medical necessity. (2.) The average exposure of the population of reproductive cells to radiation above the natural background should be limited to 10 roentgens from conception to age 30. (3.) Individual persons should not receive a total accumulated dose to the reproductive cells of more than 50 roentgens up to age of 30 years and not more than 50 additional roentgens up to the age of 40."

It is the purpose of this paper to demonstrate how radiation can be kept to a minimum in arriving at a diagnosis of intestinal obstruction in the newborn infant and to condemn unnecessary radiological procedures which not only delay but often obscure the diagnosis.

Ascaris Ileus in Children.—Obstruction of the intestinal tract by a coiled mass of Ascaris lumbricoides is a rare but serious occurrence in infancy and childhood. Because of the obstruction, necrosis, perforation, peritonitis, and death may follow. The life cycle of Ascaris has been outlined by Faust. The eggs pass into the duodenum, where the larvae are hatched. Traversing the wall of the bowel, the larvae enter the portal venous system and lymphatics. Thence they pass to the right heart and are discharged into the pulmonary capillaries, setting up a small localized intra-alveolar inflammation, simulating a Loeffler type of pneumonia. Later, after the reaction subsides, the larvae ascend the bronchial tree, pass over the epiglottis, and again enter the intestinal tract. Between the 60th and 75th day the mature worms mate and the females begin their egg-laying.

Archer and Peterson have called attention to two roentgenographic signs: (*a*) a cylindric filling defect in the jejunum and (*b*) a string-like shadow representing the barium-filled enteric canal of the parasite. Strang and Warrick later enumerated two other features, viz., linear shadows, due to adherence of barium to the worm, and evidence of disordered motility of the small bowel. Their elucidation is dependent on the use of a contrast medium. Since the segments of bowel obstructed by the parasites are distended with gas, the worms appear as elongated, linear densities of uniform caliber. Visualization is possible because the worms are in contrast with the gas in the bowel. The mass of worms within a distended segment of intestine can most often be identified on a plain film of the abdomen. In contrast to the air in the intestine, the worms appear as linear densities of uniform caliber.

News and Comment

ANNOUNCEMENTS

Residencies in Pediatric Pathology at Children's Hospital of Michigan.—Residencies in pediatric pathology are currently available at the Children's Hospital of Michigan. The pathology department is included in the Department of Laboratories, under the direction of Wolf W. Zuelzer, M.D., and is associated with an active hematology clinic and research laboratories. Clinical conferences and ward rounds are held regularly, and during the school year the hospital is the Pediatric Teaching Service of Wayne State University School of Medicine.

Positions are now available for one year, starting July, 1959. Training is recognized by the American Boards of Pediatrics, Pathology, and Radiology and by the Canadian Board of Pediatrics. The annual stipend is $2400 and room and board.

Address all inquiries to Jay Bernstein, M.D., Pathologist, Children's Hospital of Michigan, 5224 St. Antoine St., Detroit 2.

New York City Establishes "Multiple Birth Roster."—The New York City Department of Health has established a "Multiple Birth Roster." The Roster is intended to be a source of information for research workers in the fields of genetics, child development, etc. The Department will cooperate with researchers to supply them with some data which may be helpful to them to initiate genetic studies.

All multiple births involving at least two live infants are included in the Roster. All the identifying, demographic, and pregnancy information available on the birth certificate of each infant is punched on a tabulating card. A photostatic copy of the complete record of birth is also in the register, so that details not available on the punched card may be conveniently abstracted. The Roster will be kept up to date in three respects: adoption of a child, deaths during the first year of life, and data fed back to the Roster by the individual researcher. The Roster was initiated as of Jan. 1, 1958, and will be continued indefinitely. At a later date an evaluation will be made to determine whether its usage by researchers warrants its continuation.

Researchers requesting information from the Roster will be expected to adhere to such requirements as the Department may deem necessary. All requests will be reviewed as to the qualifications of the investigator and the value of the proposed study. Investigators may be asked to allocate clerical staff to assist in selecting the data requested. Facts elicited by home interviews and/or abstract of records are to be made available by the researcher to other researchers to avoid duplications of efforts.

Formal requests should be submitted to Dr. Harold Jacobziner, Assistant Commissioner for Maternal and Child Health Services, New York City Department of Health, 125 Worth St., New York 13.

Books

BOOK REVIEWS

Lehrbuch der Kinderchirurgie. By M. Grob, M. Stockmann, and M. Bettex. Price, $32.40. Pp. 775, with 876 illustrations. Intercontinental Medical Book Corporation, 381 4th Ave., New York 16, 1957.

This comprehensive textbook on pediatric surgery is the result of and contains material derived from very productive teamwork at the famous Pediatric Clinic in Zurich, Switzerland. For more than eighty years, this institution has had its own surgical department, in which the author has been active for more than twenty-five years.

The book gives symptomatology, differential diagnosis, and treatment of surgical, neurosurgical, urological, and orthopedic diseases in childhood in an incomparable manner. It lists and evaluates the traditional as well as the most modern concepts of pediatric surgery, incorporating recent Anglo-American literature. Regrettably, however, no list of references is added, although names of authors are given.

The chapters on chest surgery, including heart operations, and on cranial surgery, are unequaled in the current literature from a diagnostic as well as therapeutic point of view. The American reader will probably miss a few items, such as Allison's and Barrett's work on hiatus hernia and "short esophagus" and different facets of the intracardial valvulotomies. He may also notice that there is infrequent reference to operative statistics in various procedures, but these few omissions are generally compensated. The chapter on pre- and postoperative management leaves nothing to be desired.

Eight hundred seventy-six excellent illustrations give this volume additional value. The photographs and radiographs, selected from the author's rich material and flawlessly reproduced, are a true adventure to see. They help the reader who may encounter difficulties with the German language, although the author obviously has abstained from the use of "typical German" syntax, thus greatly facilitating translation. It would indeed be desirable to have an English translation of this great book, which undoubtedly will soon set international standards.

HORST W. FEYERABEND, M.D.

Chemical Anthropology. By Icie G. Macy and Harriet J. Kelly. Price, $3.75. Pp. 132. The University of Chicago Press, 58th St. and Ellis Ave., Chicago 37, 1957.

An attempt has been made in this book to interrelate the processes of physical growth and physiologic function with chemical growth in children (four to twelve years, inclusive). The excellent data used as the basis of this discussion have been published previously by I. G. Macy in three volumes, "Nutrition and Chemical Growth in Childhood; Vol. I. Evaluation (1942), Vol. II. Original Data (1946), and Vol. III. Calculated Data (1951)."

In the first two chapters the authors discuss briefly basic concepts of growth in children and the design of their investigation. The physical and chemical measurements which they made on children are evaluated in the next two chapters. The fifth chapter deals with various methods for the determination of body composition. Estimations of the composition of the body weight of these children are presented. The following chapter, entitled "Chemical Anthropology," in the words of the authors, ". . . is concerned with the measurement of the nutrients consumed and the chemical units laid down in the body as a whole or in its various tissues." The final chapter brings together, in an admittedly superficial manner, the various phases of the study in an attempt to find group trends and interrelationships in physical and chemical growth with particular reference to body composition.

This volume does not present any really new ideas to the reader who is familiar with the literature on the physical and physiological aspects of child development.

VIRGINIA LEE

Laboratory Applications in Clinical Pediatrics. By Irving J. Wolman, M.D. Price, $15. Pp. 1019, with no illustrations. Blakiston Company (division of McGraw-Hill Book Company, Inc.), 330 W. 42d St., New York 36, 1957.

The man who reviews a book, like the man who publishes the book concerned, never should attempt to predict the extent of the favor the book will attain. Both can be woefully wrong.

Yet the excellence of Dr. Wolman's comprehensive volume on laboratory procedures important to the pediatrician is such that enthusiasm for it is hard to restrain. It is perhaps an understatement to say that Dr. Wolman's book will, or should, become the useful possession of every student or physician interested in the treatment of children. The volume may be of less importance to the clinical pathologist, but it will nonetheless help him in the interpretation of results of tests carried out among children.

The temerity of the author in attempting to cover the whole field of clinical pediatric pathology singlehandedly must be admired. Yet the very magnitude of such a task inevitably lessens the success of the end-result, since it is impossible for one person to be expert in all fields of laboratory tests in clinical pediatrics. The consequent weakness of the book would have been avoided had the author chosen to serve as the judicious editor of a group of chapters all written by experts.

Minor deficiencies can be found. For instance, only one short sentence is given to the explanation of the thromboplastin-generation test, and the test itself is dismissed as being too complicated for routine use. Perhaps this is true, but a thorough explanation of this procedure certainly would be worth while, since if the reader can gain an understanding of the mechanism of the test he will have an excellent practical working knowledge of the first stages of clotting as these are known today.

In the discussion of porphyria some of the basic facts are obscured, namely: (1) the fact that coproporphyrins are always present in urine and are not generally reported; (2) the fact that porphobilinogen is a precursor of uroporphyrin and may be present when uroporphyrin cannot be detected, that it is also present in hepatic disease and others, and that when it is present it is not diagnostic but simply suggestive, and (3) the fact that uroporphyrin is formed only in the presence of porphyria and even then may not be present in sufficient quantities for detection.

The technique and interpretation of results of electrophoretic separation of protein fractions in serum, urine, and cerebrospinal fluid may have deserved a separate chapter, since the procedure has become routine in many laboratories. It would have been useful to point out the limitations of this technique, and at least mention might have been made that an electrophoretic pattern is pathognomonic when the nephrotic syndrome is present. The decrease in values for albumin and the increase in those for γ-globulin in the presence of disease of the liver may make flocculation reactions unnecessary, since the result can be predicted fairly accurately on the basis of the electrophoretic pattern.

Occasionally, the discussion of certain laboratory tests seems to be of more historic than practical importance, and it appears that the discussion of clinical interpretation at times is too lengthy.

Despite the foregoing minor deficiencies, some of which will be brought to the attention of the author by critical readers and most of which undoubtedly will be corrected in future editions, the volume contains much material in easily readable short chapters. The absence of illustrations and graphs is noticeable, but probably these were omitted to keep the price of the book within reasonable limits. The index is carefully done and is very complete. This factor and the bibliography of pertinent literature appended to each chapter contribute considerably to the usefulness of the book as a reference work.

GUNNAR B. STICKLER, M.D.

Manual of Pediatric Physical Diagnosis. By Lewis Abraham Barness, M.D. Price, $4. Pp. 195, with 16 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1957.

This manual represents the compilation, elaboration, and organization of material originally used in physical diagnosis courses for medical students. Dr. Barness has utilized helpful hints of many well-known pediatricians in the editing of the manuscript.

Many authorities in the allied medical specialties, such as ear, nose and throat, cardiology, neurology, and dermatology, have contributed significantly toward the completeness of this small compendium of our most basic art in medicine.

The manual is arranged in the manner in which a systematized and thorough physical examination should be carried out, namely, measurement, general appearance, examination of the head and neck, and examination of the chest. Creditably, there is a special section devoted to the examination of the newborn infant.

This manual is extremely valuable in providing a treasure of helpful hints to the neophyte physician during his pediatric clerkship and internship days. It also serves as an excellent guide to those of us responsible for training medical students and interns.

The illustrations are few but helpful and are included at pertinent points in conjunction with relevant text. Despite the appeal to the small segment of pediatricians, I recommend the manual as an excellent and well-organized reference for students, interns, and educators in pediatrics.

EDMUND C. BURKE, M.D.

Diseases of the External Ear. By B. H. Senturia, M.D. Price, $8.50. Pp. 211, with 72 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

At first glance this might seem to be a very large book about a very small subject. However, external otitis is a very common condition which in the past has not always been well managed because the causation and treatment have been extremely controversial. This remarkable book is an outstanding example of the application of scientific method to the solution of a medical problem.

The arrangement of the volume proceeds in a regular manner from a review of the pertinent literature through a consideration of the anatomy and physiology of the external ear, the bacteriology of external otitis, and reports of well-planned animal experiments to a therapeutic attack on the problems based on the investigative findings.

The treatments the author suggests therefore are logical and have proved effective, although he shows some tendency to be arbitrary and didactic in his judgments.

This book can be recommended with qualification to anyone who is faced with the problem of treating any type of external otitis and also to anyone who wishes to possess an authentic example of the scientific method in action.

HENRY L. WILLIAMS, M.D.

Hemophilia and Hemophilioid Diseases. Edited by Kenneth M. Brinkhous, M.D. Price, $7.50. Pp. 265, with 19 illustrations. University of North Carolina Press, Chapel Hill, N. C., 1957.

During the past decade astonishing advances have been achieved in the field of blood coagulation. Much of this newer knowledge has directly involved or stemmed from progress in the specific area of hemophilia and closely related hemorrhagic disorders. So rapid and often bewildering have developments been that a number of symposia on blood clotting have been held during this period in order to bring scientists and clinicians abreast of work in far-flung laboratories. A recent effort in this direction was the International Symposium held in New York in August, 1956, the proceedings of which have been published in the small volume "Hemophilia and Hemophilioid Diseases."

This symposium was attended by virtually every authority on hemophilia from Europe and England, North and South America, and Australia. The book, organized into seven major sections, each incorporating several articles and followed by a panel discussion, is a distillation of current thought on the subject. Both academic and practical aspects of this group of diseases are considered in papers on the clotting defect, genetics, diagnosis, management, orthopedic problems, and psychiatric and socioeconomic implications of hemophilia.

The interested but perhaps confused "noncoagulationist" may find consolation in the realization that even among "experts" the fundamental cause of hemophilia still remains very much in dispute. Advocates of the theory that there is a deficiency of a clotting factor (AHF) are staunchly opposed by those who maintain hemophilia is due to an excess of an endogenous anticoagulant. The latter school of thought is represented in this book by a contribution from the Seegers group. Regrettably, the case for the more widely espoused deficiency hypothesis is not championed in the printed symposium by any of its adherents. However, Verstraete, while also presenting evidence demonstrating excessive anticoagulant activity in the blood of most classic hemophiliacs, at least postulates a compromise mechanism involving a coagulant-anticoagulant conjugate.

Among the early theories on the pathogenesis of the deranged coagulation process in hemophilia the theory incriminating the platelets has been generally abandoned. In making the statement that he believes that there is a form of hemophilia in which the principal defect is in the platelets, Tocantins has apparently reviewed his old argument. One wonders whether

there is any justification, in the light of present understanding, for classification of a platelet disturbance among the hemophilias. The trend toward a broader interpretation of the hemophilioid states is also evident in the symposium by the inclusion therein of a consideration of proconvertin, a "second stage" factor. Although proconvertin (Factor V or SPCA) may be congenitally deficient and, under these circumstances, engender a severe hemorrhagic diathesis, it is not involved in the elaboration of plasma thromboplastin and logically does not belong among such "first stage" factors as AHG, PTC, PTA, and Hageman.

The unit on hemophiliac arthropathy is unusually well presented, with absorbing studies on canine pathological material and useful suggestions on orthopedic management and rehabilitation of the bone and joint complications in humans.

An interesting feature of the book is the discussion at the conclusion of each part, even though the spirited exchanges characteristic of such meetings inevitably lose much of their original flavor in editing. Also of considerable value is the glossary of synonyms and symbols which, considering the morass of terminology which has come to be associated with blood coagulation, is a necessary reference for all but the most knowledgeable.

This book should have wide appeal not only to specialists who may be most interested in isolated segments of the problem but even more so to physicians who are concerned with the total care of hemophiliac patients.

ROBERT B. ROSEN, M.D.

Hermaphroditism, Genital Anomalies and Related Endocrine Disorders. By Howard W. Jones Jr., M.D., and William Wallace Scott, M.D., Ph.D. Price, $16. Pp. 456, with 466 illustrations. The Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore, 1958.

Hermaphroditism has been recognized as a disease entity since the Grecian era. Their representation of this anomalous state, both in statue and story, forms the introduction to an informative and well-illustrated volume.

Written by a gynecologist and a urologist, the emphasis is on the diagnostic investigation and surgical repair of these genital anomalies. They have also included a thorough discussion of the present-day therapy of cryptorchism and hypospadias.

The monograph is studded with numerous illustrations and well-documented case histories.

The biochemical aspects of these endocrine abnormalities are by no means overlooked, although they are not discussed in enough detail to satisfy the specialist in this field.

This book will make a worth-while addition to the library of all those who must deal with these patients in their practice.

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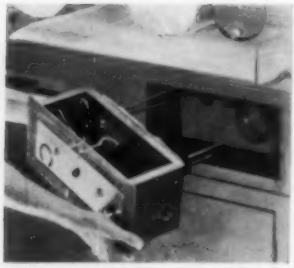

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*Zinsser, H.: Bacteriology, ed. 11, New York, D. Appleton-Century Co., Inc. 1957, p. 244.

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No Advertising "*How To Be a Parent—and Like It*" contains no advertising and refers to no authority other than the physician who uses it. Its contents have been accepted as complying with the Code for Medical Writing of the Physicians' Council for Information on Child Health.

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